Research Article

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Cost comparison of treating chronic hepatitis C genotype one with pegylated interferons in Ukraine

Abstract: Based on the pivotal trial showing no clinically relevant differences between *pegylated interferon* α-2b (Peg-α-2b) and α-2a (Peg-α-2a) combined with ribavirin for treatment of chronic hepatitis C virus (HCV) genotype 1 infection in Ukraine, a cost-minimization analysis was performed using a 1 year time horizon and both a health care and patients' perspective. A decision tree reflects treatment pathways. Drug costs were based on drug labeling and adjusted to the average body mass in Ukraine. Subgroup analysis was applied to deal with heterogeneity of patient's weight causing dose changes. A break-even price of Peg-α-2a and Peg-α-2b (based on the average dose) was calculated. Univariate sensitivity analyses and probabilistic sensitivity analysis were carried out to reflect decision uncertainty. For an average body weight, total medical costs per patient differ from US$9220 for Peg-α-2b to US$9513 for Peg-α-2a from a health care perspective, and from US$15,212 to US$15,696 from a patients' perspective. Sensitivity analyses show these results are robust. With average body weight, the break-even price of Peg-α-2b may be 7.3% higher than Peg-α-2a to have similar total costs.

Keywords: Cost minimization, Pegylated interferon, Chronic hepatitis C, Ukraine

1 Introduction

Chronic hepatitis C virus (HCV) infection is a disease with a global prevalence rate of about 180 million individuals, and every year three to four million people are newly infected [1-3]. The impact of HCV on human health is evident, as 80% of acute hepatitis C cases transform into a chronic form and 10-20% of these cases progress to hepatocellular carcinoma [3].

Currently, reliable official statistics in Ukraine are limited and mainly consist of data on acute HCV infection with jaundice and do not take into the account patients without jaundice and other clinically apparent manifestations who comprise nearly 85% of all morbid events [4, 5]. Ukraine is considered a country with a moderate prevalence of hepatitis C estimated at 1.5 to 3.5% of the population or 700,000 to 1.61 million of people [6]. Additionally, HCV infection rates among high risk groups in Ukraine, primary drugs users, homosexual males, and female sex workers, reach 40 to 60%, essentially exceeding the average global rate [7].

In Ukraine as in most countries, if treatment is indicated, the standard of HCV treatment is a combination therapy using either *pegylated interferon* α-2b (Peg -α-2b) or α-2a (Peg -α-2a) with ribavirin. Response to therapy is measured in terms of sustained virologic response (SVR),

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which is defined as undetectable HCV RNA concentrations 6 months after completion of therapy. Successful treatment of HCV depends on the virus genotype. The most common and least responsive to therapy are patients who have HCV genotype 1 (estimated 43.7% of all HCV cases or 302,000 to 704,000 people in Ukraine) [6, 8, 9].

The proportion of subjects who achieve early virologic response (defined as a 2 log or greater decrease in HCV RNA levels at week 12) and also have an SVR is called a positive predictive value. A difference in the predictability of viral clearance between Peg -α-2b + ribavirin and Peg -α-2a + ribavirin may cause a cost difference in treatment because a lower positive predictive value may result in a longer duration of therapy without achieving success.

Despite a great deal of research on this topic, transferring results from previous studies conducted in US or Western European countries may not be possible due to different socio-economic systems, health care settings, cost parameters and their relation to different perspectives, as is the case for Ukraine.

A large multicentre randomized double-blind direct comparative study (ClinicalTrials.gov number, NCT00081770) on treating patients who were infected with HCV genotype 1 with Peg -α-2b or Peg -α-2a was conducted in US on 3070 patients, applying treatment patterns similar to real-life clinical practice [10]. Treatment-naïve patients with genotype 1 without contraindications were given pegylated interferon in combination with high-dose ribavirin (on average 1000 mg per week) for 48 weeks [10-14]. During the treatment, patients'HCV-RNA was measured after 4, 12, 24, and 48 weeks, the results of which indicated intermediate treatment success. The rates of SVR and tolerability did not differ significantly between the two available pegylated interferons + ribavirin regimens, with SVR rate of 39.8% (95% confidence interval [CI], 36.8 to 42.8) for standard-dose Peg -α-2b, and 40.9% (95% CI, 37.9 to 43.9%) for Peg -α-2a. Although no statistically significant difference in efficacy between Peg-α-2a and Peg -α-2b was reported [10], drugs differed in the predictability of viral clearance (positive predictive value on week 12 was equal to 82% and 76% for Peg -α-2b + ribavirin and Peg -α-2a + ribavirin, respectively) and relapse rates that may result in differences in treatment cost.

An earlier US cost-effectiveness analysis for a hypothetical cohort of 100 HCV patients with mixed genotypes based on the level of positive predictive value [13] showed no clinically relevant difference in treatment outcome and lower cost of treatment with Peg -α-2b + ribavirin compared to Peg -α-2a + ribavirin. As stated above, differences in health care systems and perspectives of analysis may arouse a potential difficulty for transferring these US-based results (adjusting the costs and/or the cost-effectiveness estimate) to other countries [15]. Moreover, in routine clinical practice in Ukraine, an HCV genotype test is performed before treatment initiation. As treatment standards and drug instructions recommend different schemes for genotype 1 versus other HCV genotypes [16, 17], we considered that cost analysis should be also conducted separately for different HCV genotypes with clinical data based on a direct comparative trial.

No studies to our knowledge have been published on the assessment of pegylated interferons efficiency in countries belonging to the former Soviet region. Therefore, we aimed to study the costs of using Peg -α-2b in comparison to Peg -α-2a both combined with ribavirin for patients with HCV genotype 1 infection in the Ukrainian health care setting.

2 Materials and methods

For analysing the costs of using Peg -α-2b in comparison to Peg -α-2a both combined with ribavirin for patients with HCV genotype 1 infection in the Ukrainian health care setting, we used a decision analytic approach. Because no information on life-long treatment effects is available in the literature, a one year time horizon reflecting length of treatment for genotype 1 patients was defined. This relatively short time horizon makes a decision tree analysis the appropriate method to obtain accurate cost estimations.

The structure of the decision tree was based on US-study protocols' recommendations [11, 16,17]. The treatment response in the model was based on the US-based comparative trial which assessed response at 6 months after the last dose of pegylated interferon. We assumed that no additional medical services were received after treatment was discontinued or completed. Our cost analysis was conducted from both the health care and patients' perspectives (parties which are frequent payers for treatment of HCV in the Ukrainian health care setting) with only direct medical expenses included in the calculation. Although the trial [10] found no statistically significant difference in clinical effect (SVR), besides the cost minimization (per one patient and per cohort) analysis, Cost per SVR achieved was calculated since a non-significant difference in effect may have a meaningful difference in costs. Break-even price of Peg-α-2a and Peg-α-2b (the point at which cost-effectiveness results were equal) was evaluated as well.

2.1 Clinical input data

Similar to the trial [10] in the model, virologic test procedures for HCV-RNA were defined after the 4th, 12th, 24th, and 48th week of therapy initiation. After each virological test, some patients discontinued treatment with Peg -α-2b + ribavirin or Peg -α-2a + ribavirin due to treatment failure or adverse effects (Figure 1). These discontinuation numbers were retrieved from the clinical trial report (ClinicalTrials.gov number, NCT00081770; the report was provided by MSD Outcome Research), excluding those patients whose follow up data were missing. This resulted in a difference in the number of patients continuing treatment after each virological test (treatment week 12 and 24). According to the trial report, a number of patients discontinued treatment between visits on 24th and 48th weeks (2.85% for Peg -α-2b and 5.7% for Peg -α-2a). In the model, these patients were assumed to be in treatment for 36 weeks on average. Drug dose selection was based on drug labeling; a dosage of the Peg -α-2b preparation was adjusted according to the patient's weight, in contrast to a fixed dose of 180 mcg for Peg -α-2a. The analysis was conducted using the adequate dose according to drug labelling (100 mcg dose for Peg -α-2b and 180 mcg for Peg -α-2a) and to average body weight in Ukraine (74 kg).

2.2 Cost input data

Cost analysis from the health care perspective included costs of drug treatment and costs of medical personnel. While costs of the pegylated interferons were determined from state registered prices, expenses of medical personnel services were calculated according to medical services norms in Ukraine (time per patient consultation equalled 12 minutes and the number of working hours per week was 33 hours for a physician and 38.5 hours for a nurse) [18].

Patients' perspective costs were defined by out of pocket payments for drugs and laboratory tests (antibodies to HCV, quantitative prolactin) (Table 2) Patient payments for drugs were assessed from the state registered prices with the distributors and trade margins established by the Order of the Cabinet of Ministers of Ukraine from 24.09.2012 (Table 1). A test for antibodies to HCV (usually conducted once on treatment initiation) costs $13.77 (exchange rate 1 USD = 7.99 UAH on 01.01.2014 by the National Bank of Ukraine) [19].

The costs related to ribavirin (weight dependent) were not considered in the model in both perspectives because due to policies of the manufacturers of both drugs, ribavirin is provided free of charge by the companies when purchasing pegylated interferons. Because the reported adverse event profiles for both of the drugs were similar [10], the costs associated with adverse events were not included.
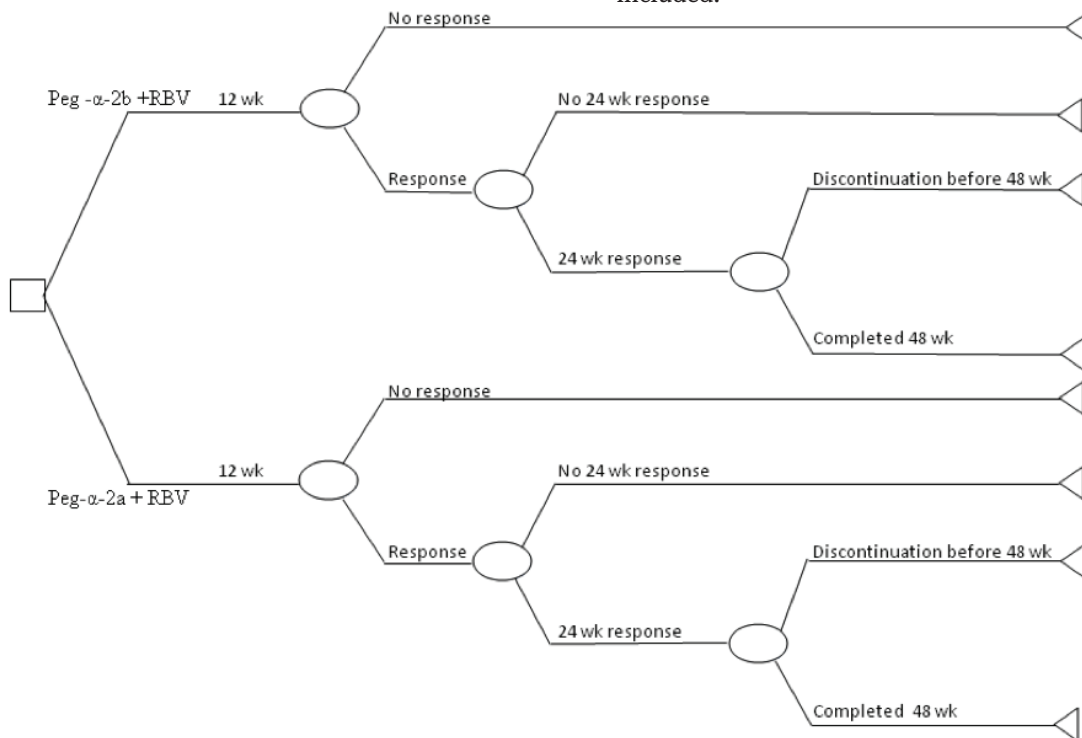

Figure 1: Decision tree comparing two strategies for genotype 1 HCV treatment

Table 1: Cost of drug treatment: HCV genotype 1.

Regime	Drug costs (Health care perspective), $*	Drug costs (Patient's perspective), $**
Peg-α-2a (180 mcg)	264.02	316.82
Peg-α-2b (120mg)	277.20	332.64
Peg-α-2b (50mg)	265.00	318.00
Peg-α-2b (80mg)	268.20	321.84
Peg-α-2b (100mg)	275.90	331.08
Peg-α-2b (150mg)	283.05	339.66

* Prices as given on the website of the Ministry of Health of Ukraine (http://www.moz.gov.ua/ua/portal/register_prices_drugs/) on 01.01.14
** Drugs prices with the distributors and trade margins established by the Order of Cabinet of Ministers of Ukraine #880 from 24.09.2012

2.3 Sensitivity analysis

To reflect the uncertainty inherent in the research, univariate sensitivity analyses were performed using alternative assumptions regarding providers' costs and diagnostics' costs. To reflect decision uncertainty, probabilistic sensitivity analysis (PSA) (1000 draws using Monte Carlo simulation) were carried out. In the PSA, cost of drugs and medical personal were varied in range ±20%, and costs of the laboratory analysis on quantitative prolactin were derived from the minimum to maximum price lists of the laboratories providing their services in Ukraine (Table 2) [19].

For valuing parameters in the model from the original trial data, patients with missing outcomes were excluded. For instance, the confidence interval (CI) with 95% CI for the parameter "number of patients who completed 48 week treatment" was not available, while the 95% CI for negative and positive 48 weeks responders was almost similar between both drugs compared. We assumed that the 95% CI for 48 weeks completers had a similar range to positive 48-weeks responders for both strategies (±4% Peg-α-2b and ±3.75% for Peg-α-2a). The number of 48-week completers caused changes in cohort drug costs, laboratory cost, and medical personal costs.

We used subgroup analysis to deal with heterogeneity of patient's weight causing changes in doses of Peg-α-2b according to drug labelling; less than 40 kg: 50 mcg of Peg-α-2b; 40-64 kg: 80 mcg of Peg-α-2b; 65-75 kg: 100 mcg of Peg-α-2b; 75-85 kg: 120 mcg of Peg-α-2b; more than 86 kg: 150 mcg of Peg-α-2b.

Ethical approval: The conducted research is not related to either human or animals use.

3 Results

The results of the cost analysis are presented in the Table 3. Total medical costs per one patient (accounting the average body mass in Ukraine) varied from $9220 for Peg-α-2b to $9513 for Peg-α-2a from a health care perspective, and from $15,212 for Peg-α-2b to $15,696 for Peg-α-2a from a patient's perspective. The total cost for an estimated population of patients with HCV genotype 1 in Ukraine varied from a minimum of $2.780 billion (for Peg-α-2b) to $2.868 billion (for Peg-α-2a) and to a maximum of $6.487 billion (for Peg-α-2b) to $6.693 billion (for Peg-α-2a) from a health care perspective. Using break-even point analysis, it was defined that a price of Peg-α-2b should be 7.3% higher than Peg-α-2a to have equal/similar total costs. The cost per successfully treated patient, defined as having an SVR, was lower for Peg-α-2b in comparison to Peg-α-2a from patients' perspective and almost similar between treatments from a health care perspective.

The results of univariate sensitivity analyses in genotype 1 patients are shown in Table 4. The costs of medical assistance and laboratory tests did not have a significant impact on total cost difference. For the subgroup analyses, the cost difference between Peg -α-2b and Peg -α-2a varied from 6.90% (weight less than 40 kg) to 0.56% (weight more than 86 kg) from a health care perspective, and from 6.81% (weight less than 40 kg) to 0.63% (weight more than 86 kg) from a patient's perspective. The costs per patient and costs per SVR in accordance to the mode trial dose of Peg-α-2b [10] were slightly higher than using body mass-based calculation for Ukraine, though a general cost difference in favour of Peg-α-2b was observed.

PSA results showed an average cost difference of 2.19 and 2.25% from the health care and patients perspectives respectively (median 3.84%, std. error = 1.37% from the health care; median 3.80%, std. error = 1.34% from the patients' perspective) in favour of Peg -α-2b + ribavirin. Mean SVR rates as a result of the PSA (40.08% for Peg -α-2b + ribavirin and 41.03% for Peg -α-2a + ribavirin) were similar to the deterministic data confirming the validity of the calculations.

Table 2: Decision-tree model input parameters

Parameter, measure	Value in deterministic model	Source	Value in PSA	Source
The proportion of patients who completed 48 week Peg 2b, %	47.89%	[16]	43.89-51.89%	ClinicalTrials.gov number, NCT00081770
The proportion of patients who completed 48 week Peg 2a, %	55.26%	[16]	51.51-59.41%	ClinicalTrials.gov number, NCT00081770
SVR Peg-2a, %	40.90%	[16]	37.90-43.90%	McHutchison et al. (2009) [10]
SVR, Peg-2b,%	39.80%	[16]	36.80-42.80%	McHutchison et al. (2009) [10]
Average monthly salary of a medical worker, $*	$296.00	National statistics service of Ukraine, 2013 [20]	$236.80-355.20	20% variation from the data in deterministic model
Cost of the laboratory test on quantitative prolactin, $*	$84.05	[19]	$47.56-$120.53	Dolkar's initiative for Viral Hepatitis patients care, 2009 [20]

* Exchange rate UAH/USD is 7.99 on 01.01.2014 by National Bank of Ukraine

Table 3: Economic outcomes per patient infected with HCV genotype 1

Regimen, weekly	Health Care Perspective		Patient's perspective	
	Total costs, US$	Cost/SVR, US$	Total costs, US$	Cost/SVR, US$
Peg-α-2a (not weight dependent,180 mcg)	9513	23,202	13,969	28,539
Peg-α-2b (expected dose consumption in Ukraine, average 100mcg)	9220	23,165	15,212	28,352
Peg-α-2b (mode trial dose,120mcg)	9264	23,276	15,283	28,482

Table 4: Sensitivity of cost differences to uncertainty in input values (per patient)

Parameter estimates	Cost difference (Health care perspective), US$	Cost difference (Patient's perspective), US$
Base-case result	293	360
Patients' weight		
<40kg	657	797
>86 kg	54	74
Cost of medical assistance		
Maximum value	293	-
Minimum value	293	-
Cost of HCV laboratory test		
Maximum value	-	304
Minimum value	-	312

4 Discussion

The results from this cost comparison suggest that therapy with Peg -α-2b + ribavirin may be less costly than Peg -α-2a + ribavirin for patients with genotype 1 HCV infection in cases in which no statistically significant difference in the rates of SVR achieved is assumed [10]. As the positive predictive value is higher for Peg -α-2b among patients with genotype 1 with no effect on clinical outcome (SVR), it leads to a lower number of patients receiving treatment when successful outcome is not possible, and so to lower cost per successful treatment because the probability of successful treatment is equal between the strategies. The results of the sensitivity analyses showed that input parameters such as cost of medical assistance and laboratory tests do not affect the results of the base case analysis substantially. Because Peg -α-2b allows weight-based dosing, the subgroup analyses showed the economic advantage may be higher for patients with lower weight and lower for patients with higher weight than average. Adjustment to the patient's body weight can lead to additional cost reductions from both patients' and health care perspectives.

Due to possible price changes for pharmaceutical products on the Ukrainian market as a result of negotiation policy of distributors and producers participating in state tender purchases (no reimbursement currently exists in Ukraine), we consider that the break-even price instead of the actual price should be considered to determine cost efficiency of the product in Ukraine. Price variation because of negotiations is a frequent action on the Ukrainian state pharmaceutical market, and a similar strategy was announced by the Ministry of Health of Ukraine in relation to access to hepatitis treatment [21]. The higher positive predictive value of Peg -α-2b may lead to cost savings as long as the price of Peg -α-2b is not more than 7.3% higher than Peg -α-2a.

Treatment with pegylated interferon + ribavirin for chronic hepatitis patients is considered to be a standard therapy in many countries. In Ukraine, application of this scheme competes with interferon + ribavirin treatment (from 40 to 60% of the prescriptions by experts' estimates [personal communication with treating physicians]). As final clinical outcomes of HCV treatment such as virus eradication and prevention of death and progression to cirrhosis and hepatocellular carcinoma occur over a long period of time and are difficult to measure, SVR can serve as a surrogate indicator whether the treatment goal has been achieved [22]. Several studies indicate the association of SVR with improvements in liver histology, probability of developing liver decompensation, quality of life,

and survival [23-28]. While the majority of the population of Ukraine cannot afford expensive drug products [29], patient access to treatment with pegylated interferon plus ribavirin is crucial in the Ukrainian health care setting.

The methods used here, a decision analysis using data from one pivotal trial, allowed us to derive essential clinical parameters for valuing the model parameters (such as number of patients continuing the therapy after each measurement of virologic control). Another direct comparative trial focused on measuring SVR as an outcome of treatment of naïve patients with genotype 1 HCV (instead of mixed genotypes). These data were not included in our model as no significant clinical difference in the limited treatment groups (37 patients in each one) was reported [30]. Since these results are similar, we do not expect differences in the results of economic evaluation if these additional data were to be incorporated to value parameters in the model.

While the largest comparative trial was used for clinical input data, it should be noted that the previous systematic review [31] provided assessment of efficacy with pegylated interferon treatment for patients with a mixed genotype, while no genotype-specific comparison was conducted. Meanwhile, for treatment naïve HCV patients with genotype 1, there were only four studies were SVR was used as efficacy measure. Two of these trials, conducted by Sinha et al and Yenice et al., included a limited number of patients, enrolling 42 and 80, respectively [30,32]. Two studies by Rumi et al. and Ascione et al., both conducted in Italy (178 patients and 181 patients with genotype 1 HCV, respectively), reported the same probability (p=0.04) for Peg -α-2a + ribavirin to be clinically superior to Peg -α-2b + ribavirin [33,34]. The current cost-minimization analysis was based on the clinical data from the largest trial available which showed no statistically significant difference between treatment arms. The weighted pooled data from the three trials has shown almost similar SVR rates for genotype 1 patients (41.5% for Peg -α-2a + ribavirin and 40.2 % for Peg -α-2b + ribavirin) to the data used in the current study [10,33,34]. While this adjustment has no impact on the results of the current cost-minimization study, the cost for one SVR reached remained equal for both drugs. Several economic studies on treatment of naïve patients with chronic HCV infection have been published in different countries [12-14,35]. The most recent study on pegylated interferons was conducted for the US [13], applying similar methodology as our study, defining the cost-efficacy of Peg -α-2b + ribavirin scheme for patients with HCV (genotypes 1,2,3). Though the aim of the study was similar, the perspective of the US-study was one of a managed care organization. Thus, using the

transferability criteria for cost-effectiveness estimates as stated by the ISPOR taskforce on transferability [15], it may not be applicable for Ukraine, where major treatment costs for HCV treatment are partially covered by patients' payments and partially by government through state purchases. Despite the difference in perspectives, Malone et al. reached the similar conclusion, stating that treating with Peg -α-2b + ribavirin provides cost savings in comparison to Peg -α-2a + ribavirin because fewer patients are treated beyond 12 weeks when achieving SVR is unlikely [13]. The indicated study suggested that although both Peg -α-2a and Peg -α-2b have demonstrated similar SVR overall, for genotype 1, there is a significant difference in early virologic response rates. Thus, using Peg -α-2a + ribavirin for genotype 1 patients may cause more treatments' consumption for the patients' cohort without additional health benefit over those treated with Peg -α-2b.

A number of other economic studies compared treatment with interferons and pegylated interferons for genotype 1 HCV treatment-naïve patients [12,14,35], confirming cost-effectiveness of the latter one. A study in Spain, conducted by Buti et al. , also defined treatment with Peg -α-2b + ribavirin as the optimal strategy which includes adjustment to the patient's body weight for 48 weeks and good therapeutic compliance [12]. Siebert et al. concluded that Peg -α-2b + ribavirin could reduce the incidence of liver complications, prolong life, improve quality of life, and be cost effective for the initial treatment of HCV in patients in Germany[35]. Sullivan et al. evaluated cost-effectiveness of Peg -α-2a + ribavirin versus traditional interferon, coming to the similar conclusion on efficiency pegylated interferons in patients in the US [14].

In our analysis comparing two pegylated interferons, we observed similar results with the study of Malone et al. , though due to differences in sources of clinical outcomes (SVR rates), cost components, and prices, the total costs were different [11]. Thus, the results from our study may help to assess costs for HCV genotype 1 treatment in Ukraine and may be more easily transferable to other former Soviet countries.

This analysis suggests that use of Peg -α-2b + ribavirin may be preferred to Peg -α-2a + ribavirin in treatment of genotype 1 HCV infected patients due to lower costs associated with treatment, given the earlier finding of comparable clinical efficacy. Use of Peg -α-2b + ribavirin in comparison to Peg-α-2a + ribavirin could lead to a cost reduction of $88 to $206 per patient if the treatment for all the cohort of genotype 1 HCV patients is provided. Price of Peg -α-2a would have to be lower to achieve similar efficiency to Peg -α-2b.

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