Effects of Recombinant Erythropoietin in Palliative Treatment of Unselected Cancer Patients

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ABSTRACT

Purpose: The purpose is to evaluate relationships between objectively assessed exercise capacity and subjectively assessed scoring of physical functioning and well-being after erythropoietin treatment in cancer patients on palliative care.

Experimental Design: Unselected cancer patients (n = 108) who experienced progressive cachexia were randomized to receive either anti-inflammatory treatment alone (indomethacin) or recombinant erythropoietin plus indomethacin to prevent the appearance of disease-induced anemia and thereby protect patients’ exercise capacity. Follow-up investigations of nutritional status, exercise capacity, and health-related quality of life assessed by SF-36 and the European Organization for Research and Treatment of Cancer QLQ-C30 were compared.

Results: Effective treatment by erythropoietin on top of basal whole body anti-inflammatory treatment was confirmed and indicated by time course changes of biochemical, physiologic, and nutritional objectives, whereas individual self-reported scoring of physical functioning and general health did not indicate a clear-cut effectiveness, particularly at moderately subnormal hemoglobin levels.

Conclusions: Discrepancies between objective and subjective self-reported measures may be either fundamental or indicate scoring limitations for evaluation of therapeutic results. Present results demonstrate a clinical benefit of erythropoietin treatment in cancer patients with subnormal to normal hemoglobin levels, whereas the patients’ own subjective scoring was insufficient to sense such improvements. The discrepancy may be either fundamental or methodological but emphasizes the importance to document therapeutic outcome in both subjective and objective perspectives in palliative care of cancer patients.

INTRODUCTION

Patients with cancer cachexia due to progressive disease suffer usually from appearing anemia, which is an inducer and promoter of weight loss, depressed exercise capacity, and altered energy homeostasis (1, 2). However, treatment of cancer patients with recombinant erythropoietin can protect patients from becoming anemic during disease progression, which prevents an expected decline in exercise capacity with potential implications for health-related quality of life (HRQL; ref. 3) and hypoxia-related events (4). Positive effects after provision of recombinant erythropoietin to cancer patients are in part expected from physiologic perspectives because exercise capacity should be proportional to circulating amount of hemoglobin, at least within a large range of blood concentrations. However, it remains less clear to what extent physiologic and biochemical improvements are directly translated into improved self-reported HRQL, although information on significant and positive relationship between HRQL and anemia is well established in enrolled cohorts of patients with and without chemotherapy-induced anemia (5, 6). In addition, it has appeared questionable to what extent improved self-assessed functioning and well-being are equivalent to clinical significance in various studies (7). Therefore, this article evaluates to what extent physiologic improvements, due to improved cardiovascular function after recombinant erythropoietin treatment to unselected cancer patients, are translated into improved self-assessed well-being and functioning evaluated by validated instruments of HRQL (social functioning (SF)-36 and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30).

MATERIALS AND METHODS

As previously reported, 108 cancer patients, mainly suffering from gastrointestinal malignancy, were randomized at the Department of Surgery, Sahlgrenska University Hospital (Göteborg, Sweden) for treatment with either oral indomethacin alone (50 mg twice per day) or the combination of indomethacin (50 mg twice per day) and s.c. injections of recombinant erythropoietin α (range of 12,000 to 30,000 IU per week, Eprex; Janssen-Cilag, Stockholm, Sweden) injected by a nurse three times a week until blood hemoglobin concentration was normalized within reference values for healthy individuals (3, 8). Eprex treatment was thus instituted when blood hemoglobin concentration fell below lower limits of normal hemoglobin concentration (128 g/L for men, 120 g/L for women) and was maintained until hemoglobin was normalized during iterated courses (3). This means that some patients never received erythropoietin, although they were randomized to this treatment.
group. Oral iron substitution was provided to erythropoietin-treated patients when serum-iron concentration was <15 μg/L (Duroferon, Astra-Hässle, Sweden) containing folic acid; (75% of the erythropoietin-treated patients). Patients at risk during follow-up in the study (erythropoietin treated) and control group (indomethacin treated) were reported elsewhere (3, 9). Indomethacin treatment continued until death or the patients were unable to take the tablet (9). Study and control patients received no other specific treatment for their malignancy. Analgesics (paracetamol and morphine) were provided according to individual needs. None of the study and control patients received blood transfusions during the follow-up period.

Inclusion criteria were insidious or ongoing weight loss due to generalized malignant disease with a solid tumor type. Patients should not have any other efficient or established tumor treatment available and must have completed the most recent applied tumor therapy > 2 months before inclusion. Expected patient survival time was estimated to be ≥6 months. Exclusion criteria were reported elsewhere (3).

Follow-up Measurements

All patients were treated according to the protocol and followed until death. All measurements were performed at inclusion and then after 2 to 4, 6 to 8, and 10 to 30 months, depending on survival (every second month). Physiologic variables at rest included heart rate, systolic and diastolic blood pressure, respiratory rate, and energy expenditure (10). All patients gave informed consent before randomization. A group of nurses remained in continuous contact with all patients and their families to assist and respond to questions. The use of analgesics was assessed before and during follow-up.

Nutritional Assessment

Nutritional state (body weight, length, triceps skin fold, arm muscle circumference, and handgrip strength) were measured by a specially trained nurse as described previously (9). Body composition was measured by the dual-energy X-ray absorptiometry technique (11). Body fat and lean tissue mass were analyzed using the extended research mode of software with time course changes in body composition of study and control patients as reported previously (3). Food intake was assessed by a four day validated diary (11). The overall caloric intake was 1927 ± 693 kcal/day and 1823 ± 588 kcal/day (mean ± SD) in study and control patients, respectively, during follow-up.

Blood Tests

Blood chemistry included hemoglobin concentration, erythrocyte particulate concentration, mean erythrocyte volume, mean corpuscular hemoglobin concentration, S-Fe, total iron-binding capacity, WBC count, thrombocyte count, electron spin resonance, C-reactive protein (CRP), S-albumin, serum electrolytes, S-creatinine, and serum liver function tests (3). The average CRP levels were 40 ± 5 μg/L in erythropoietin-treated patients during follow-up and 28 ± 6 μg/L in control patients (3). Plasma insulin-like growth factor I was determined by radioimmunoassay from Medigastion (Zeutlinger, Germany).

Indirect Calorimetry

Resting energy expenditure was measured by indirect calorimetry (Deltratrac; Datex, Helsinki, Finland) in the morning after an overnight fast (12). Average resting energy expenditure was 1412 ± 32 kcal/day in erythropoietin-treated patients during follow-up and 1566 ± 4 kcal/day in the controls (3).

Exercise Test

Exercise testing and simultaneous measurements of oxygen uptake and carbon dioxide production were carried out as described in detail elsewhere (3).

HRQL Questionnaires

Two self-administrated questionnaires were used to measure HRQL.

Medical Outcomes Study Short-Form Health Survey (SF-36). The SF-36 contains 36 questions that assess eight aspects of patients’ HRQL: physical functioning, role-physical functioning, bodily pain, general health, vitality, social functioning, role emotional functioning, and mental health. Responses to questions within scales were summed and linearly transformed to scale scores that range from 0, representing poor health status, to 100 representing optimal health status. The Swedish version has been validated and normative data have been presented for the general Swedish population (13).

EORTC QLQ-C30 (+3) Questionnaire. The EORTC QLQ-C30 (version 1.0) is a 30-item core questionnaire intended for assessment of HRQL among cancer patients developed by the EORTC Quality of Life Study group (14). Reference data from the general populations in Norway and Sweden have been published (15, 16). The questionnaire is composed of five functional scales: physical functioning (five questions), role functioning (two questions), cognitive functioning (two questions), and social functioning (two questions). There are three symptom scales: fatigue (three questions), nausea and vomiting (two questions) and pain (two questions), and there are six single items on dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties. Two global questions are asking about the patient’s health status and overall HRQL. All scales and single-items’ measure ranges in score from 0 to 100. A high score for the functioning scales and the global health status and HRQL represents a high level of functioning/health status, whereas a high score for the symptom/item scales represents a high level of symptoms/problems. The HRQL scores were calculated according to the EORTC QLQ-C 30 scoring manual (17).

Study Design and Statistics

Randomization and Measurement before Treatment. Randomization was performed by a computerized algorithm accounting for a number of variables (18): tumor type, tumor stage, earlier tumor treatment (surgery, chemotherapy, and radiotherapy), expected survival in months, age, sex, and nutritional state (19); body weight, weight loss, serum albumin concentration, arm muscle circumference, triceps skin fold, resting energy expenditure, liver function tests (serum bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatases), serum creatinine, blood hemoglobin concen-
transam, erythrocyte sedimentation rate, Karnowsky’s index (20), and previous intake of analgesics. Statistical testing was performed according to intention to treat only. No patients were censored during follow-up (21). Statistical comparison among blood concentrations and exercise testing in study and control patients were made by ANOVA (Statview version 5.0; Abacus) and included all observations from the start of the protocol and the entire follow-up period (3). The comparison between study and control patients on HRQL scales was performed with the log-rank technique (Mantel Cox) and included all information on all patients from the start until the end of follow-up. Within group alterations, over time, were tested by regression analysis. Survival, evaluated by Kaplan-Meier analysis, has been reported elsewhere without negative effect by erythropoietin (22, 23). \( P < 0.05 \) was regarded statistically significant.

The study was approved by the Committee for Ethics, Medical Faculty, Göteborg University (Göteborg, Sweden).

RESULTS

Fig. 1 illustrates how cancer patients are protected from anemia when treated with erythropoietin as reported elsewhere (3). Erythropoietin treatment translated into maintained or even increased maximum exercise power (Fig. 2), even confirmed within ranges of normal hemoglobin concentrations (Fig. 3). Thus, blood hemoglobin concentrations between 130 and 169 g/L were related to significantly higher \( (P < 0.01) \) maximum exercise power compared with patients who experienced lower hemoglobin concentrations even close to the normal range (120 to 129 g/L; Fig. 3). There was a highly significant correlation between blood hemoglobin concentrations and maximum exercise power, although with a large variation around the regression line (Fig. 4). This relationship contrasted to a more tight correlation between whole body oxygen uptake and exercise power (Fig. 5). These regressions (Figs. 4 and 5), based on measurements in unselected patients, were more variable than corresponding relationships in individual patients as expected (Fig. 6).

Figs. 7 and 8 show that self-reported physical functioning was significantly more \( (P < 0.05) \) dependent on blood hemoglobin levels than the subjective scoring of general health (Fig. 8) because the two regressions had statistically significantly different slopes \( (P < 0.05) \). By contrast, the relationship between objectives as either hemoglobin or maximum exercise power and the physical functioning scale (SF-36) showed the highest fit to a curve-linear function (Fig. 9), whereas general health (SF-36) was proportionally more related to exercise power (Fig. 10). These observations imply that patients could lose up to 30% of their normal exercise power without subjective appreciation of decreased physical functioning. Similar regressions were obtained when comparable scales were used in calculations on data from either SF-36 or EORTC-QLQ-C30 instruments (data not shown).

![Fig. 1 Time course changes in blood hemoglobin concentration in study and control patients treated as described in Materials and Methods. ■, erythropoietin-treated patients; □, indomethacin-treated patients, \( P < 0.01 \).](image1)

![Fig. 2 Time course changes in maximum exercise power in study and control patients treated as described in Materials and Methods. ■, erythropoietin-treated patients; □, indomethacin-treated patients \( P < 0.001 \).](image2)

![Fig. 3 Distribution of the relationship between blood hemoglobin concentration (g/L) and maximum exercise power (W) based on observations from all study and control patients during follow-up [hemoglobin (Hb), g/L]. *, \( P < 0.01 \) versus all other groups.](image3)
Erythropoietin-treated cancer patients showed a trend to significant improvement in general health (SF-36; Table 1), compared with untreated cancer patients with significant anemia. Analysis on the same cohort of patients by the EORTC instrument revealed no clear-cut significant improvements by erythropoietin treatment (Table 2). Thus, self-reported physical functioning did not discriminate significantly among study and control patients by neither SF-36 or the EORTC QLQ-C30 instrument. Apparently, a number of anemic patients did not score their physical functioning to be significantly reduced until exercise power decreased below 100 to 110 W (Fig. 9).

Measures of systemic inflammation (CRP and erythrocyte sedimentation rate) did not differ during follow-up between study and control patients, whereas erythropoietin-treated patients had significantly better nutritional state (total body fat and lean body mass but not plasma insulin-like growth factor I) at the end of the follow-up period as reported (3). Multiple regression analyses to identify predictive factors of subjectively assessed physical functioning (SF-36) and general health (SF-36) are demonstrated in Table 3. Variables on systemic inflammation (hemoglobin and CRP), nutritional state (insulin-like growth factor I, whole body fat, lean body mass, and caloric intake), and integrated physiology (maximum exercise power) showed that several of these factors predicted physical functioning and general health ($P < 0.0001$). Thus, CRP, maximum exercise power, whole body fat, lean body mass, and caloric intake were all significant factors to predict subjectively scored physical functioning and general health. The only principal difference between physical functioning and general health was that alterations in whole body fat accounted for alterations in physical functioning but not in the scoring of general health. Also, when any of these statistically significant factors were

![Fig. 4](image1)

**Fig. 4** The relationship between hemoglobin concentrations (g/L) and maximum exercise power (W) in all study and control patients during follow-up ($r = 0.36, Y = 0.85x - 19.9, P < 0.0001$).

![Fig. 5](image2)

**Fig. 5** The relationship between whole body oxygen uptake (mL) and maximum exercise power (W) from observation on all study and control patients during follow-up ($r = 0.84, Y = 0.07x - 3.61, P < 0.0001$, $n = 205$).

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![Fig. 6](image3)

**Fig. 6** The relationship between exercise power and whole body oxygen uptake in five unselected patients. The correlation coefficients were all $>0.96$ ($P < 0.001$) determined by linear regression analysis.

![Fig. 7](image4)

**Fig. 7** The relationship between blood hemoglobin concentrations and self-reported physical functioning (PF) in all study and control patients during follow-up ($r = 0.30, Y = 0.48x - 0.56, P < 0.001$).
omitted in the computations, blood hemoglobin concentration appeared a significant predictor ($P < 0.03$; data not shown).

Maximum exercise capacity was significantly predicted by lean body mass ($P < 0.001$), whole body fat ($P < 0.002$), and plasma insulin-like growth factor I ($P < 0.004$; data not shown).

**DISCUSSION**

Patients with malignant disease may become anemic due to several interacting factors. In surgical practice, it is common that such patients receive blood transfusions to attenuate symptoms associated with anemia in cancer, as fatigue, hampered tissue regeneration and compromised immunity. The availability of recombinant erythropoietin has dramatically changed the possibility to either prevent or treat anemia (24, 25), although recent findings have indicated that recombinant erythropoietin may be pluripotent with effects beyond stimulation of blood formation (26–31). In our previous study, we demonstrated that early provision of recombinant erythropoietin to randomized unselected cancer patients was efficient to prevent development of anemia in both males and females on palliative care (3). This regimen was also effective to support patients’ exercise capacity evaluated by a standardized walking test as re-illustrated in the present report. Our clinical impression is that patients on recombinant therapy, overall, do well compared with untreated patients who were on anti-inflammatory (indomethacin) medication only. Positive effects after erythropoietin treatment have been reported by others for patients on either chemotherapy or radiation in controlled studies (4, 6, 27, 28, 32, 33), although hesitance has been provided (5, 22, 23, 34–37). However, chemotherapy-induced anemia may only seemingly be similar to tumor-induced anemia (33) because different mechanisms may explain insufficient blood formation after drug toxicity compared with systemic inflammation with hormonal and cytokine alterations explaining cachexia. Besides, effects of hematopoietic growth factors on cancer growth, proliferation, and chemosensitivity are still open questions (38). Therefore, it was deemed interesting to evaluate how alterations in self-reported quality of life (HRQL) and performance status relate to objective evaluations of integrative physiology during progressive disease with and without anemia in patients randomized to erythropoietin treatment (39, 40). Our interest of this was based on observations in other groups of patients revealing that one may adapt in subjective evaluations of performance status. Thus, young patients who had experienced gut resections early in life, with subsequent appearance of alterations in body composition and nutritional state, scored their own physical fitness inappropriately high compared with normative data. Normal aging may also be a factor with adaptations that change a patient’s own appreciation of normality (41). Such phenomena may be appropriate adaptive mechanisms within the central nervous system to conform to new conditional levels secondary.

Fig. 8 The relationship between blood hemoglobin concentrations and self-reported general health (GH) in all study and control patients during follow-up ($r = 0.20$, $Y = 0.28x - 14.6$, $P < 0.002$).

Fig. 9 The relationship between maximum exercise power (W) and self-reported physical functioning (PF) in all study and control patients during follow-up ($r = 0.49$, $Y = 0.58x - 0.002 \times 2 + 27.5$, $P < 0.001$).

Fig. 10 The relationship between maximum exercise power and self-reported general health (GH) in all study and control patients during follow-up ($r = 0.37$, $Y = 0.22x + 32.2$, $P < 0.001$).
to disease factors (coping), or one may simply forget how it feels to be healthy. Thus, evaluation of medical treatment as well as health and disease interventions should ideally include both subjective and objective assessments of outcome. Validated instruments for HRQL assessments and standardized testing of integrative physiology may offer such possibilities (39, 42).

In cancer research, several instruments for HRQL are available (39). In the present study, we chose to use a general instrument for assessment of health and performance (SF-36) and a more cancer-specific instrument (EORTC QLQ-C30). Alternatives for standardized testing of integrative physiologic functioning may be several depending on type of function being appropriate in various settings. On the basis of the present protocol, it was assumed that walking is appropriate for evaluation of either maximum walking distance or maximum exercise power. In previous studies, we elaborated different kinds of exercise testing such as bedridden ergometry or traditional bicycle ergometry (43). Thus far, walking seems to be the most feasible in this respect, integrating a number of natural functions in the musculoskeletal system such as respiration, circulation, cardiac function, and mental abilities to conduct a maximum effort during the unpleasant sensation of dyspnea and accompanied hypoxia in muscles of aging and disease. Simultaneous measurements of whole body oxygen consumption and exercise power may also allow estimation of energy effectiveness or the energy cost for power (3).

Our present results demonstrate that whole body oxygen consumption is strictly related to the amount of work produced on individual patient basis (Fig. 6), and it is also highly proportional to produced power on a group basis in patients as expected (Fig. 5). These correlations are important because older and unhealthy individuals suffer from a variety of disorders that may influence on their ability to walk and withstand standardized testing with reproducibility. Thus, variations around regressions of the relationships between blood hemoglobin, exercise power, and various self-assessments include a number of confounding factors (lean body mass, body fat, and plasma hormones), which may or may not influence on medical outcome and the possibility to correctly judge the effectiveness of therapies under test. For example, by comparing the regressions for maximum exercise power in relationship to either oxygen uptake or blood hemoglobin concentrations, it appears (as expected) that oxygen consumption is a more limiting factor for physical performance than oxygen availability reflected by blood hemoglobin concentration, although they are not independent factors and may incorporate unknown covariates (36). New information in this study is that variations in blood hemoglobin concentrations, within rather narrow ranges of normal blood hemoglobin in male and female patients, represent a limiting factor for exercise capacity (Fig. 3), which may be relevant for physical functioning in daily activities. A similar finding was observed between objective and subjective assessments of performance but at a less precise level. Thus, walking could detect limitations in exercise performance among patients even within the normal range of blood hemoglobin concentrations, whereas patients’ own subjective assessments only sensed a reduced physical capacity below subnormal blood hemoglobin

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concentrations. This fact does necessarily not represent a discrepancy to previous studies reporting improved HRQL with increasing hemoglobin levels after erythropoietin treatment because such studies typically evaluated patients with more advanced anemia due to chemotherapy (8, 29, 32), whereas the present study evaluates disease-related anemia.

Interestingly, it was observed that different scales of HRQL, which should directly or indirectly reflect performance as physical functioning and general health, were differently related to exercise power. Surprisingly, a large number of patients could lose up to one third of their maximum exercise power without appreciation in self-assessments of physical functioning, whereas their scoring of general health was more proportional to performance over a large range of declining concentrations.
exercise power. This illustration emphasizes the necessity to evaluate medical treatments in several dimensions, both objective and subjective.

Traditionally, self-assessed HRQL is evaluated in study groups and compared with either controls or normative cohorts. Results presented in that way (Tables 1 and 2) demonstrate unexpectedly that comparatively few items of HRQL came out statistically different by SF-36 or by the more cancer-specific instrument (EORTC). Whether this represents a low sensitivity of the test instruments, insufficient statistical power, or that confounding or unknown factors correctly attenuated dimensions of subjective assessments is difficult to know. However, the combined statistical evaluation among patient groups over time by the log-rank technique or ANOVA and within groups over time by regression analysis indicates that some subjective improvements may have occurred in response to erythropoietin treatment of anemia for improvement of HRQL in cancer patients because blood hemoglobin appeared statistically predictive when other significant factors were omitted in the calculations as also observed in uni- and multivariate analyses reported by others (44). Our findings may rather indicate that other regimens such as anti-inflammatory treatment and nutritional support interventions may just be more powerful to provide compared with treatment of anemia for improvement of HRQL in cancer patients with progressive disease. The fact that anti-inflammatory treatment and nutritional support are individually effective in cachectic cancer patients can prevent the appearance of anemia, which is associated with a clear-cut improvement or protection of patients’ maximum exercise power during palliative care (3).

It is not likely that a surprisingly low likelihood of beneficial effects on HRQL by erythropoietin treatment to our cancer patients with progressive disease was just a matter of statistical power because multifactorial analyses on the same data with physical functioning and general health as dependent variables demonstrated that a variety of factors in different combinations explained the variance in scores of self-assessment (Table 3). Interestingly, it appeared that blood hemoglobin levels were not a significant factor in combinations with other variables such as inflammation, nutrition, and body composition. This does not exclude the possibility that anemia is a significant factor behind reduced HRQL in palliative treatment of cancer patients because blood hemoglobin appeared statistically predictive when other significant factors were omitted in the calculations as also observed in uni- and multivariate analyses reported by others (44). Our findings may rather indicate that other regimens such as anti-inflammatory treatment and nutritional support interventions may just be more powerful to provide compared with treatment of anemia for improvement of HRQL in cancer patients with progressive disease. The fact that anti-inflammatory treatment and nutritional support are individually effective interventions to improve objectively assessed status and performance in comparable cohorts of cancer patients has been reported by us (45, 46).

In conclusion, the present evaluation on randomized patients illustrates that provision of recombinant erythropoietin to cachectic cancer patients can prevent the appearance of anemia, which is associated with a clear-cut improvement or protection of patients’ maximum exercise power during palliative care (3). However, such physiologic improvements were not clear-cut translated into improved subjective scoring of physical functioning or sensation of well-being when evaluated by a global or cancer specific instrument for self-assessed HRQL. Although our results may be expected (47) or unexpected (48), the present study emphasizes the importance to evaluate therapeutic effec-

### Table 3

Regression coefficients in multiple regression analysis of PF and GH (SF-36) and variables of systemic inflammation (Hb and CRP) nutritional state (IGF-I, whole body fat, LBM, and caloric intake) and integrated physiology (maximum exercise capacity)

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<td>CRP</td>
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<tr>
<td>Hb</td>
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<td>Fat total</td>
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NOTE. PF: \( r = 0.69, P < 0.0001, n = 116 \); GH: \( r = 0.57, P < 0.0001, n = 113 \).

Abbreviations: PF, physical functioning; GH, general health; Hb, hemoglobin; ns, not significant; IGF-I, insulin-like growth factor I; LBM, lean body mass.
tiveness of medical treatments in several dimensions, both objective and subjective.

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Effects of Recombinant Erythropoietin in Palliative Treatment of Unselected Cancer Patients

Elisabet Lindholm, Peter Daneryd, Ulla Körner, et al.


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