GUIDELINES FOR ARSENIC TRIOXIDE (Trisenox™) TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA (APL)

BACKGROUND

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia characterized by the chromosomal translocation t (15:17) resulting in the formation of the promyelocytic leukemia gene -all trans retinoic acid alpha (PML-RARα) fusion protein. Once one of the most fatal types of leukemia, patients with APL now have much improved prognosis, largely in part due to the discovery of two clinically effective treatment strategies: all-trans retinoic acid (ATRA) and arsenic trioxide.

INDICATIONS

Arsenic trioxide has recently been approved for use in Canada, and is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL), that is refractory to or has relapsed from retinoid and anthracycline therapy, and whose APL is characterized by the presence of the t(15;17) translocation or promyelocytic leukemia-retinoic-acid-receptor alpha (PML-RARα) gene expression. Until recently, Princess Margaret has been obtaining approval for use of arsenic trioxide on a per patient basis from the Special Access Program (SAP). Arsenic trioxide is now approved for use in Canada, and is currently used at Princess Margaret for induction in patients with relapsed/resistant APL, and rarely for maintenance therapy of APL in patients who are intolerant to ATRA therapy. This review includes data on the use of arsenic trioxide as first line treatment of APL in addition to its current approved use in relapsed/resistant APL.

Previous treatment of first-line APL at Princess Margaret was as follows:

Induction (given as inpatient): ATRA 45mg per m² per day for 28 days, daunorubicin 60mg per m² on Days 1-3 (or Days 6-8), and cytarabine 100mg per m² per day on Days 1-7. Cytarabine is omitted in patients older than 60 years old with white blood count greater than 10 x 10⁹ per litre.

Consolidation 1 (given as outpatient): ATRA 45mg per m² per day for 28 days, daunorubicin 60mg per m² on Days 1-3, and cytarabine 100mg per m² per day on Days 1-7.

Consolidation 2 (given as outpatient): ATRA 45mg per m² per day for 28 days, daunorubicin 45mg per m² on Days 1-3, and cytarabine 1.5 grams per m² every 12 hours for 6 doses on Days 1, 3, and 5.

The Leukemia group at Princess Margaret requests that arsenic trioxide be used according to Cancer Care Ontario's New Drug Funding Program, with a slight modification to give arsenic as a 7 day treatment when given as inpatient, and as a 6 day treatment for when given as an outpatient. For low-risk patients, the first 10 days of induction will be given in inpatients and the rest of the treatment will be given as an outpatient.

CLINICAL STUDIES

Arsenic trioxide in relapsed/resistant APL
The introduction of arsenic trioxide as a treatment option for APL has created a paradigm shift in the treatment of APL-relapsed patients. Most of the data on the use arsenic trioxide in APL is in relapsed patients.

The use of arsenic trioxide in relapsed APL has been compared to other treatment modalities. Au and colleagues\(^5\) conducted a retrospective chart review of 153 APL cases, in which they compared the 3 major treatment strategies for relapsed APL (n = 54): chemotherapy (n = 19), chemotherapy plus bone marrow transplantation (n = 14) or chemotherapy plus arsenic trioxide therapy (n = 21). The authors did not mention the doses and duration of chemotherapy used for induction of the second CR (CR2), however, in the chemotherapy plus arsenic trioxide group, arsenic trioxide 10mg IV daily until remission and idarubicin IV 72mg/m\(^2\) in 9 divided doses over 3 months were used. Patients who relapsed after arsenic trioxide therapy (n = 8) were further treated with IV arsenic trioxide (10mg/day) and oral ATRA (45mg/m\(^2\)/day) until CR3, followed by consolidation with arsenic trioxide + ATRA, given every 14 days for 4-6 weeks for 6 cycles. Of the 3 regimens, chemotherapy was associated with a CR2 rate of 47% and treatment related mortality (TRM) of 53%. Chemotherapy plus bone marrow transplantation (BMT) had a CR2 rate of 64% and a TRM of 36%. The CR2 rate of chemotherapy plus arsenic trioxide therapy was 100% with no TRM. The overall survival (OS) for the three protocols at 2 years was 23% for chemotherapy, 43% for chemotherapy and BMT and 82% for chemotherapy plus arsenic trioxide (p = 0.0004).

In a randomized controlled trial of arsenic trioxide monotherapy vs. arsenic trioxide plus ATRA therapy in 20 patients with relapsed APL, Raffoux and colleagues\(^6\) demonstrated a CR2 rate of 80% after one arsenic trioxide cycle with or without ATRA. The dose of arsenic trioxide used in this trial was 0.15mg/kg/day IV until CR achievement, or severe toxicity (grade 2 to 4 depending on the affected organ), or arsenic serum concentrations of 10-5M or greater, or to a maximum of 56 doses. The dose of ATRA used was 45mg/m\(^2\)/day starting on day 1 of arsenic trioxide administration until CR achievement. Adverse effects were similar between the two groups, with the exception of headaches, which was more common in the arsenic trioxide + ATRA group. QT prolongation was transient and moderate. The most severe adverse event was APL-related differentiation syndrome (7/20), of which 6 of these patients required dexamethasone and amsacrine chemotherapy for treatment.

In another trial investigating the use of arsenic trioxide monotherapy for recurrent APL, Lazo and colleagues\(^7\) reported its use in 12 patients with recurrent APL previously treated with ATRA ± anthracycline chemotherapy ± ARA-C received IV arsenic trioxide 0.15mg/kg/day until CR was achieved or 60 doses were administered. All 12 patients reached CR, with a median time of 52 days. Post-remission therapy varied, 4 patients received arsenic trioxide monotherapy for consolidation, 6 patients received arsenic trioxide in combination with other agents (chemotherapy or allogenic bone marrow transplant) and 2 patients received chemotherapy alone. After a median time of 98 weeks, 67% of patients were alive and in CR. Side effects were well tolerated, with the exception of 2 patients who developed Grade 2 and 3 peripheral neuropathy, of which one required discontinuation of therapy.

Soigent et al\(^8\) reported the safety and efficacy of arsenic trioxide use in 40 patients experiencing a first (n = 21) or ≥ second (n = 19) of APL. Patients enrolled had relapsed from anthracycline based induction chemotherapy with either ATRA or 9-cis retinoic acid. Patients were given IV arsenic trioxide 0.15mg/kg/day until bone marrow (BM) remission was observed, to a cumulative maximum of 60 doses. Patients achieving clinical response (CR) received a onetime dose of IV arsenic trioxide (0.15mg/kg/day) as consolidation 3-4 weeks after induction therapy, with the option to receive up to four additional cycles of arsenic trioxide therapy as maintenance. 18 patients received arsenic trioxide maintenance therapy. CR was observed in 85% (35/40) of patients, with a median time to clinical CR of 59 days. The 18 month Kaplan-Meier estimates of overall survival (OS) and risk free survival (RFS) was 66% and 56%.
respectively. 68% (27/40) of patients reported grade 3 or 4 adverse effects, the most commonly reported ones were nausea (75%), cough (65%), fatigue (63%), fever (63%), headache (60%), vomiting (58%), tachycardia (55%), diarrhea (53%), hypokalemia (50%) and skin rash (43%). Serious or life threatening events were noted in 48% of patients, the most common being hypokalemia (13%), hyperglycemia (10%) and neutropenia (10%). The authors did not specify the remaining serious adverse effects.

Arsenic trioxide in as first-line treatment of APL

There is now increasing data on the use of arsenic trioxide as initial treatment in APL (induction, consolidation and maintenance therapy) \(^9,10,11,12,13\). The most compelling data is from a recent publication by Lo-Coco et al. which was a phase 3, multicenter trial comparing ATRA (all-trans retinoic acid) plus chemotherapy group to ATRA plus arsenic trioxide in patients with APL classified as low-to-intermediate risk (white-cell count, \(\leq 10 \times 10^9\) per liter). Patients were randomly assigned to receive either ATRA plus arsenic trioxide for induction and consolidation therapy or standard ATRA – idarubicin induction therapy followed by three cycles of consolidation therapy with ATRA plus chemotherapy, and maintenance therapy with low-dose chemotherapy and ATRA. \(^13\) The study was designed as a noninferiority trial to show that the difference between the rates of event-free survival at 2 years in the two groups was not greater than 5%. Complete remission was achieved in all 77 patients in the ATRA – arsenic trioxide group who could be evaluated (100%) and in 75 of 79 patients in the ATRA – chemotherapy group (95%) (P = 0.12). The median follow-up was 34.4 months. Two-year event-free survival rates were 97% in the ATRA – arsenic trioxide group and 86% in the ATRA – chemotherapy group (95% confidence interval for the difference, 2 to 22 percentage points; P<0.001 for noninferiority and P = 0.02 for superiority of ATRA – arsenic trioxide). Overall survival was also better with ATRA – arsenic trioxide (P = 0.02). As compared with ATRA – chemotherapy, ATRA – arsenic trioxide was associated with less hematologic toxicity and fewer infections but with more hepatic toxicity. Grade 3 or 4 neutropenia and thrombocytopenia lasting more than 15 days were significantly more frequent both during induction therapy and after each consolidation course in the ATRA – chemotherapy group than in the ATRA – arsenic trioxide group. Counting together fever of unknown origin and documented infectious episodes occurring during either induction or consolidation therapy, we recorded 26 episodes in the ATRA – arsenic trioxide group and 59 episodes in the ATRA – chemotherapy group (P<0.001). A total of 43 of 68 patients in the ATRA – arsenic trioxide group (63%) and 4 of 69 patients in the ATRA – chemotherapy group (6%) had grade 3 or 4 hepatic toxic effects during induction or consolidation therapy (for patients in the two groups) or during maintenance therapy (for patients in the ATRA – chemotherapy group) (P<0.001). In all cases, the toxic effects resolved with temporary discontinuation of arsenic trioxide, ATRA, or both or with temporary discontinuation of chemotherapy during the maintenance phase (for patients in the ATRA – chemotherapy group).

Illeland et al. used a combination of all-trans retinoic acid (ATRA), anthracycline-based chemotherapy, and arsenic trioxide in an APML4 phase 2 protocol in patients with high risk APL. For induction, arsenic trioxide in combination with ATRA and idarubicin, were given. Consolidation comprised 2 cycles of ATRA and arsenic without chemotherapy, followed by 2 years of maintenance with ATRA, oral methotrexate, and 6-mercaptopurine. Of 124 evaluable patients, there were 4 (3.2%) early deaths, 118 (95%) hematologic complete remissions, and all 112 patients who commenced consolidation attained molecular complete remission. The 2-year rate for freedom from relapse is 97.5%, failure-free survival 88.1%, and overall survival 93.2%. Compared with their previously reported ATRA/idarubicin-based protocol (APML3), APML4 patients had statistically significantly improved freedom from relapse (P = .006) and failure-free survival (P = .01). The use of arsenic trioxide in both induction and consolidation for these patients achieved excellent outcomes despite a substantial reduction in anthracycline exposure.
PHARMACOLOGY

The mechanism of action for arsenic trioxide is not completely understood. It is thought that arsenic trioxide degrades and cleaves the PML-RARα oncoprotein (a protein involved in the leukemogenesis of APL), which leads to de-repression of transcription suppression and restoration of PML nuclear body structure. The blockade of other signaling pathways is also released, and the anti-apoptotic effect of PML-RARα is lost, resulting in the restoration of normal cell signaling³.

PHARMACOKINETICS⁴

Arsenic trioxide, when placed in an aqueous solution, hydrolyses into arsenious acid (As³⁺), the pharmacologically active species of arsenic trioxide. Monomethylarsonic acid (MMAV) and dimethylarsinic acid (DMAV) are the main metabolites of As³⁺.

Distribution: Volume of distribution (As³⁺): 562 L; widely distributed throughout body tissues

Metabolism: As³⁺ is methylated to MMAV and DMAV by hepatic methyltransferases.

Half-life elimination: As³⁺: 10-14 hours; MMAV: ~32 hours; DMAV: ~72 hours

Time to peak: As³⁺: At the end of infusion; MMAV and DMAV: ~10-24 hours

Excretion: Urine (MMAV, DMAV, and 15% of a dose as unchanged As³⁺)

ADVERSE EFFECTS

ECG Changes: Use of arsenic trioxide can cause QT interval prolongation, torsades de pointes and complete atrioventricular block. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. 40% of these patients had at least one ECG tracing with a QTc interval > 500msec, and QTc prolongation occurred between 1 and 5 weeks after arsenic trioxide infusion and returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In a similar study¹⁴, clinical data and serial ECGs from 99 patients with advanced malignancies who received 170 courses of arsenic trioxide in either a phase I or phase II investigational study were reviewed. Prolonged QT intervals developed in 38 patients (26 patients had intervals > 500 milliseconds). Compared with baseline, the heart rate—corrected (QTc) interval was prolonged by 30 to 60 milliseconds in 36.6% of treatment courses, and by more than 60 milliseconds in 35.4% of patients.

Torsades des pointes: In a case report of 3 patients with leukemia treated with arsenic trioxide¹⁵, torsade de pointes was noted in 3 of the 19 patients enrolled in a clinical trial of arsenic trioxide treatment of hematological malignancies. Pretreatment QTc intervals and echocardiography were normal in all 3 patients. In the first patient, a 29 year old man with acute myeloid leukemia (AML) with prior anthracycline exposure (72mg/m² IV idarubicin, 36mg/m² IV mitoxantrone) received 20mg of arsenic trioxide daily. Premature ventricular contractions and ventricular tachycardia developed with prolongation of QTc interval on electrocardiography (ECG). ECG returned to normal after treatment with lidocaine, bretylium, magnesium and multiple cardioversions, but ventricular tachycardia with the morphology of torsades de pointes recurred and cardioversion was unsuccessful. In the second case, a 79 year old woman with relapsed myelodysplastic syndrome evolving into AML with no prior anthracycline exposure developed prolonged QTc interval on day 16 of arsenic trioxide therapy (20mg daily IV). This was successfully treated with intravenous magnesium and correction of her potassium level. In the last patient, a 43 year old man with refractory AML after 4 cycles of induction (72mg/m²² IV idarubicin, 36mg/m²² IV mitoxantrone) developed prolongation of QTc interval after 7 days of treatment with arsenic trioxide(10mg IV daily). His
QTc intervals gradually shortened after discontinuing arsenic trioxide, but the patient was intubated for respiratory distress 12 days after the start of arsenic trioxide and developed ventricular tachycardia with the morphology of torsades des pointes; multiple cardioversions were unsuccessful.

**APL Differentiation Syndrome:** Characterized by fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions with or without leukocytosis, APL differentiation syndrome can occur in some patients treated with arsenic trioxide therapy. In an analysis of the incidence, characteristics, prognostic factors, and outcome of 739 APL patients treated with ATRA plus idarubicin in 2 clinical trials, the onset of clinical manifestations of the differentiation syndrome was found to follow a bimodal distribution with 46% of patients developing clinical manifestations within one week and 38% developing symptoms between the third and fourth week of starting ATRA or arsenic trioxide.

**Hyperleukocytosis (white blood cell count greater than 10 x 10^9/L during treatment):** Arsenic trioxide use has been associated with the development of hyperleukocytosis. In the Soignet et al trial, hyperleukocytosis (WBC ≥ 10 x 10^9/L) was reported in 50% of patients receiving IV arsenic trioxide therapy (0.15mg/kg/day). In patients with leukocytosis, the peak WBC occurred at a median of 19 days after receiving their first dose of arsenic trioxide (range 3 – 36 days). However, no patient required additional treatment with cytotoxic agents or leukapheresis. For hyperleukocytosis in low-risk APL patients with white blood cell count 10 – 50 x 10^9/L, give hydroxyurea 500 mg PO four times daily and titrate up if needed. If white blood cell count greater than 50 x 10^9/L, give hydroxyurea 1000 mg PO four times daily and titrate up if needed. Discontinue hydroxyurea when white blood cell count drops to less than 10x10^9/L.

**Other significant adverse effects:** A brief overview of other adverse effects reported with arsenic trioxide use is as detailed below:

- **Gastrointestinal:** Nausea (75%), abdominal pain (58%), vomiting (58%), diarrhea (53%), sore throat (35%), constipation (28%), anorexia (23%), appetite decreased (15%), weight gain (13%)
- **Central nervous system:** Fatigue (63%), fever (63%), headache (60%), insomnia (43%), anxiety (30%), dizziness (23%), depression (20%), pain (15%)
- **Neuromuscular & skeletal:** R rigors (38%), arthralgia (33%), paresthesia (33%), myalgia (25%), bone pain (23%), back pain (18%), limb pain (13%), neck pain (13%), tremor (13%)
- **Hematologic:** Anemia (20%, Grade ¾: 5%), Disseminated intravascular coagulation, Grade 3 and 4 (8%), febrile neutropenia (13%; grades 3/4: 8%) thrombocytopenia (18%; grades 3/4: 13%)
- **Hepatic:** ALT increased (20%; grades 3/4: 5%), AST increased (13%; grades 3/4: 3%)
- **Renal:** Renal failure (8% ), Renal impairment (8% )
- **Respiratory:** Cough (65%), dyspnea (53%; grades 3/4: 10%), epistaxis (25%), hypoxia (23%), pleural effusion (20%), sinusitis (20%), postnasal drip (13%), upper respiratory tract infection (13%), wheezing (13%)

**CONTRAINDICATIONS**

Arsenic trioxide is contraindicated in patients who are hypersensitive to arsenic.

**MONITORING REQUIREMENTS**

**NOTE:** If corrected QT interval (QTc) is greater than or equal to 500 msec, hold arsenic, continue daily ECG monitoring, and administer arsenic trioxide when QTc is less than 500 msec, and as directed by the Electrophysiology or Cardiology services.

Contact physician or NP if Potassium (K⁺) concentrations are below 4 mmol/L and Magnesium (Mg²⁺) less than 0.9 mmol/L. If K⁺ and Mg²⁺ levels are significantly lower, levels must be re-checked after giving
boluses prior to arsenic administration. Patients receiving diuretics should have more frequent electrolyte replacement. If syncope, rapid or irregular heartbeats occurs, patient should be assessed for electrolyte abnormalities.

Prior to initiating therapy: 12-lead ECG, creatinine, serum electrolytes (potassium, calcium, magnesium). Preexisting electrolyte abnormalities should be corrected and if possible, drugs known to prolong QTc should be discontinued.

During therapy and subsequent infusions:

Vital signs (heart rate, blood pressure, respiratory rate, and oxygen saturation) for initial infusion, at baseline, every 15 minutes x 1 hour, then every 30 minutes until completion and post-infusion. For subsequent infusions, vital signs (heart rate, blood pressure, respiratory rate, and oxygen saturation), at baseline, every 30 minutes, then prior to discharge.

Check patient’s weight; report to physician or nurse practitioner if weight gain is more than 1 kg in 24 hours as it may indicate APL differentiation syndrome. Patients should be weighed daily during induction only, and there is no need to wait for patient weight to be available before preparing drug. During consolidation, patient weight (used for arsenic dose calculation) should be obtained in clinic prior to treatment on Day 1 of each cycle. APL differentiation symptoms include: fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions with or without leukocytosis. Treating APL differentiation symptoms promptly with high dose steroids (dexamethasone 10mg IV BID) until abatement of these signs and symptoms is strongly recommended.

Liver function tests (AST, ALT, ALP, bilirubin) are assessed a minimum of once weekly.

ECGs, complete blood count, potassium, magnesium calcium and serum creatinine are assessed daily until frequency altered by physician or nurse practitioner; twice weekly is the minimum frequency. Physician or advanced practice nurse should review ECG and bloodwork before proceeding with drug administration.

Drugs for treatment of anaphylactic reactions must be readily available.

DRUG INTERACTIONS

No formal assessments of pharmacokinetic drug-drug interactions between arsenic trioxide and other drugs have been conducted. The methyltransferases responsible for metabolizing arsenic trioxide are not members of the cytochrome P450 family of isoenzymes.

DOSAGE AND ADMINISTRATION

At Princess Margaret, arsenic use and patient estimates are as follows:

For APL First Line and Relapsed/Refractory Induction:

- Low to Intermediate Risk (WBC ≤ 10 x 10⁹/L)
  - Arsenic, in combination with ATRA, is administered intravenously at a dose of 0.15mg/kg daily until complete remission. An estimated 16-18 patients will have low-risk APL each year, with each patient receiving about 30 doses for induction.

- High Risk (WBC > 10 x 10⁹/L)
Arsenic, in combination with ATRA, is administered intravenously at a dose of 0.15mg/kg daily on days 9 to 36. An estimated 8-9 patients will have high-risk APL each year, with each patient receiving about 28 doses for induction.

For APL First Line and Relapsed/Refractory Consolidation:

- Low to Intermediate Risk (WBC \( \leq 10 \times 10^9/L \))
  - Arsenic, in combination with ATRA, is administered intravenously at a dose of 0.15mg/kg/day on Days 1 to 6, 8-13, 15 to 20, and 22 -23 (20 doses), and 4 weeks off, for a total of 4 cycles. Each patient at will receive approximately 80 doses.

- High Risk (WBC > 10 \( \times 10^9/L \))
  - Two cycles of arsenic, in combination with ATRA, are administered as follows:
    - Cycle 1 (3-4 weeks after the end of induction): Arsenic 0.15 mg/kg/day days 1 to 6, 8 to 13, 15 to 20, 22 to 27, and 29-32 (28 doses).
    - Cycle 2 (3-4 weeks after the end of consolidation cycle 1): Arsenic 0.15mg/kg/day IV on Days 1 to 6, 8 to 13, 15 to 20, 22 to 27, and 29 (25 doses)

NOTE: For low-risk patients, induction will be given as inpatient treatment for the first 10 days and the rest of the treatment will be given as an outpatient.

Arsenic is reimbursed by CCO at a cost of $53 per mg. If used according to above, anticipated wastage from partial vials should be minimal.

All-trans retinoic acid (Vesanoid®) is covered by the Ontario Drug Benefit Exceptional Access Program or by private plans.

Patients with renal impairment: Severe renal impairment (Clcr <30 mL/minute): Use with caution (systemic exposure to metabolites may be higher); monitor closely for toxicity. Use in dialysis patients has not been studied.

Patients with hepatic impairment: Severe hepatic impairment (Child-Pugh Class C): monitor closely for toxicity.

Administration:

Arsenic trioxide diluted in 250mL 0.9% Sodium Chloride is administered IV over 2 hours for the first dose. If patient tolerates first cycle, infuse subsequent doses over 1 hour. If patient experiences acute vasomotor reactions during infusion, care for patient symptomatically, and double infusion time for remainder of infusion (i.e., if current infusion time is over 2 hours, extend infusion time to 4 hours; if current infusion time is over 1 hour, extend infusion time to 2 hours). For patients who had prior reactions, infuse subsequent doses over 2 hours.

Arsenic trioxide may be administered via a peripheral or central line.

All-trans retinoic acid (ATRA) dosing:

Low-risk APL:

Induction:

ATRA 45 mg/m²/day will be administered orally in two equally divided doses and rounded to the nearest
10 mg increment, starting on day 1. ATRA treatment will be continued until hematological complete remission (CR) or for a maximum of 60 days.

Consolidation:
ATRA 45 mg/m²/day will be administered orally in two equally divided doses and rounded to the nearest 10 mg increment. Treatment will be administered on Days 1-14 and off from Days 15-28 for a total of 7 courses (last course administered on weeks 25 - 26).

High-risk APL:

Induction:
ATRA 45 mg/m²/day will be administered orally in two equally divided doses and rounded to the nearest 10 mg increment, on Days 1-36.

Consolidation 1 (3-4 weeks after the end of induction):
ATRA 45 mg/m²/day will be administered orally in two equally divided doses and rounded to the nearest 10 mg increment on Days 1-28.

Consolidation 2 (3-4 weeks after the end of consolidation cycle 1):
ATRA 45 mg/m²/day will be administered orally in two equally divided doses and rounded to the nearest 10 mg increment on Days 1-7, 15-21, 29-35.

CONCLUSIONS

Arsenic trioxide has been demonstrated to have good efficacy when used as a treatment for first line and relapsed/resistant APL in patients with low to intermediate risk and high risk APL. We recommend the routine use of arsenic trioxide at the Princess Margaret-UHN restricted to first-line and relapsed/resistant APL.

Please refer to communication and schedule documents for protocol specifics.

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