Late Cardiovascular Toxicity Following Chemotherapy for Germ Cell Tumors

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Abstract

The introduction of cisplatin-based chemotherapy has transformed germ cell tumors (GCTs), the most common malignancy to affect young adult men, into a highly curable cancer, even in the setting of advanced disease. However, over the past decade, the success of these chemotherapy regimens in curing GCTs has been temporized by an increasing recognition of their important late toxicities, such as cardiovascular disease. The relative risk of coronary artery disease in this population is particularly elevated within the first 10 years of follow-up, when patients are still in their 30s and 40s, which are age groups often considered too young to experience cardiovascular events. Two hypotheses have been proposed to explain the association between chemotherapy and cardiovascular disease in this population. The direct hypothesis asserts that chemotherapy causes diffuse endothelial damage, including in the coronary arteries, gradually leading to cardiovascular disease. In contrast, the indirect hypothesis proposes that chemotherapy leads to an increased incidence of cardiovascular disease risk factors, such as hypertension, hyperlipidemia, and the metabolic syndrome, which in turn enhance the risk of cardiovascular disease. This article summarizes the data on the association between chemotherapy (predominantly cisplatin-based) and the development of cardiovascular disease among GCT survivors, and reviews the evidence supporting both mechanistic hypotheses. In addition, recommendations are provided for the management of GCT survivors who received cisplatin-based chemotherapy and are therefore at risk for cardiovascular toxicity. (*JNCCN* 2012;10:537–544)

Together, cancer and cardiac disease account for half of all deaths each year in the United States.¹ Although as causes of death, these 2 illnesses are considered mutually exclusive, in life they often coexist and evidence is accumulating that they are linked. This issue is particularly relevant to cancer survivors, who represent a rapidly growing population. Today, nearly two-thirds of all patients with cancer are expected to be alive 5 years after their diagnosis, and in the United States the number of cancer survivors now exceeds 11 million.²

Germ cell tumors (GCTs), the most common tumor to affect men between ages 15 and 35 years, have long been considered a model for the curable malignancy,³ because even patients with widely metastatic disease can be cured with cisplatin-based chemotherapy with or without surgery. Unfortunately, over the past 2 decades, data have emerged linking chemotherapy, particularly cisplatin, with several late toxicities, with cardiovascular disease chief among them. Much of the evidence for this association has arisen from follow-up studies of patients with advanced GCTs, who, because of their young age at diagnosis, nearly universal treatment with cisplatin, and long life expectancy after therapy, are at particular risk for late toxicities. This article reviews the available evidence on the association between chemotherapy (predominantly cisplatin-based) and cardiovascular disease. The evidence supporting each of the 2 proposed mechanisms for this association, known as the direct and indirect vascular damage hypotheses,⁴ is summarized and recommendations for how to approach cisplatin-treated GCT survivors, given their potential cardiovascular risks, are provided. Additional late toxicities occurring in this population after treatment were reviewed elsewhere.^{4,5}

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Defining the Risk

Remarkably, within only 1 year of the initial publication⁶ describing the success of cisplatin-based chemotherapy in curing testicular GCTs, a case report was published documenting unexpected obstructive coronary atherosclerosis identified on autopsy in 2 patients in their 20s who were treated for and died of advanced GCTs.⁷ Additional case reports of cardiovascular events ensued, but estimates of the incidence of this toxicity were not possible until recently. In 2000, Meinardi et al.⁸ reported on the cardiovascular outcomes of 87 GCT survivors, all younger than 50 years of age (median age, 41 years) at time of evaluation, who had received cisplatin-based chemotherapy at a single center in the Netherlands, had been followed for at least 10 years since completion of chemotherapy, and had never received radiation. With a median follow-up of 14 years, 5 patients (6%) had experienced documented myocardial infarction or angina, the latter consisting of ischemia noted on stress testing and/or significant disease noted on coronary angiography. The relative risk was 7 times that of age-matched controls who had stage I testicular GCTs and had been treated with orchiectomy alone.

Huddart et al.⁹ identified a similar 7% incidence of angina, myocardial infarction, or sudden cardiac death among 360 patients treated with chemotherapy in the United Kingdom, with an age-adjusted relative risk of 2.6 compared with patients with GCTs treated with surgery alone. In a subsequent retrospective study of a nationwide cohort of 2339 5-year GCT survivors treated in the Netherlands between 1965 and 1995, investigators found an increased incidence of coronary heart disease, defined as myocardial infarction or angina, compared with age and sex-matched data in the general Dutch population, with a standardized incidence ratio of 1.17 (95% CI, 1.04–1.31).¹⁰ With a median follow-up of 18 years, the absolute incidence of cardiac events was 6.3% among the 664 patients treated with chemotherapy alone. The calculated 20-year actuarial risk for all patients was 10.3% for myocardial infarction or angina, and 7.2% for myocardial infarction alone.¹⁰ This risk was 2-fold higher than the age-matched general population up to 54 years of age, and for patients of all ages within 5 to 9 years of completing treatment.¹⁰ Relative risks for older patients (age > 54 years) and those followed for longer periods (≥ 10 years) were less

significant. In a follow-up study, the relative risk was also higher when subdiaphragmatic radiation was combined with chemotherapy compared with chemotherapy alone (standardized incidence ratio [SIR], 2.3; 95% CI, 2.6–4.9 vs. SIR, 1.4; 95% CI, 1.6–3.1).¹¹ Together, these data, which are summarized in Table 1^{8–10,12} (older and smaller studies were reviewed elsewhere^{9,13}), suggest premature coronary artery disease may be a significant cause of late morbidity and mortality in GCT survivors, warranting further exploration of the pathophysiology and impact of clinical interventions.

Mechanisms

Chemotherapy-Induced Endothelial Dysfunction (Direct Hypothesis)

Accumulating evidence shows that direct vascular injury plays an important role in the pathophysiology of late cardiovascular effects of chemotherapy in GCT survivors. Early on, Raynaud's phenomenon (RP) was identified in 22 of 60 (37%) GCT survivors treated with bleomycin and vinblastine (with or without concurrent platinum-based therapy).¹⁴ Subsequent prospective observational studies estimate that the prevalence of RP in GCT survivors according to self-reporting or physician assessment ranges from 25% to 61%.^{15–19} Symptoms generally begin within 4 to 12 months of chemotherapy, and although many patients experience resolution or at least improvement over time, persistent RP lasting up to 20 years has been reported in up to 25% of patients.²⁰

Investigations into the mechanism of chemotherapy-induced RP have also revealed abnormal vascular findings in patients with GCTs. In one study, abnormal hand arteriograms were noted with diffuse arterial narrowing and vascular cutoffs.¹⁴ A subsequent study of GCT survivors 4 to 9 years post-completion of cisplatin, vinblastine, and bleomycin (PVB) found that although 44% of patients reported symptoms of RP, 100% showed an exaggerated vasomotor response to cold.²¹ Similar prolonged vasoconstriction responses to cold among patients treated with PVB have been observed in other studies.²² Abnormal nailfold capillary morphology has also been identified on videomicroscopy in greater than 90% of patients with GCTs treated with vinblastine, bleomycin, adriamycin, and cisplatin.¹⁸

Table 1 Incidence and Relative Risk of Coronary Artery Disease in Chemotherapy-Treated Patients in Select Studies Since 2000

Author (Year)	CAD Definition	N	Dates of Chemotherapy	Median Follow-Up (Range)	CAD Incidence	CAD Relative Risk
Meinardi et al. ⁸ (2000)	MI or angina with proven myocardial ischemia	87	Before 1987	14 y (10–20 y)	5 (5.7%)	7.1 ^a
Huddart et al. ⁹ (2003)	MI, angina, or SCD (based on medical records or GP communication)	390	1982–1992	9.7 y (0–20 y)	26 (6.7%)	2.6 ^{b,c}
Van den Belt-Dusebout et al. ¹⁰ (2006)	MI or angina (based on medical records or GP communication)	664	1965–1995	18.4 y (5.0–38 y) ^d	42 (6.3%)	1.35 ^a
Haugnes et al. ¹² (2010)	MI or angina (81% of patients with angina had cardiac revascularization)	364	1980–1994	19 y (13–28 y) ^d	52 (5.6%)	2.6 ^b

Abbreviations: CAD, coronary artery disease; GP, general practitioner; MI, myocardial infarction; SCD, sudden cardiac death.

^aObserved/event ratio compared with general male Dutch population.

^bCompared with patients with testicular cancer managed with surveillance (no chemotherapy or radiation) in the same cohort.

^cRelative risk by age-adjusted logistic regression.

^dMedian follow-up time reflects the authors' entire study cohort, not limited to only those treated with chemotherapy.

Regarding specific causal agents, bleomycin has the strongest association with RP. In a study of 395 patients with good-risk nonseminomas randomized to receive 4 cycles of etoposide and cisplatin with (BEP) or without bleomycin (EP), 8% of patients in the BEP arm developed acute RP compared with none in the EP arm.²³ Vinblastine and cisplatin have also been implicated as contributing to this toxicity.^{15–18} For example, higher rates of digital ischemia were identified in patients treated with cisplatin compared with those who were not (41% vs. 21%).¹⁴ The cumulative dose of chemotherapy and the prevalence of conventional risk factors for peripheral arterial disease, such as hypertension or smoking, may also play a role.^{15,16}

In vitro studies and laboratory findings further support a direct mechanism of cardiovascular disease through chemotherapy-induced endothelial dysfunction. For example, exposure of endothelial cells to cisplatin or bleomycin in vitro leads to endothelial cell cytokine release and cytotoxicity.^{24,25} Microalbuminuria, indicative of systemic vascular dysfunction due to generalized endothelial dysfunction, is present in an increased number of young GCT survivors. Furthermore, microalbuminuria independently predicts for vascular events, including stroke and myocardial infarction.²⁶ In one study of GCT survivors (median age, 37 years) with a median follow-up of 7 years, microalbuminuria was present

in 12% of patients treated with chemotherapy but in fewer than 1% of those treated with orchiectomy alone or healthy age-matched controls.²⁰ With a longer median follow-up of 14 years, microalbuminuria was detected in 22% of patients with GCTs treated with cisplatin-based chemotherapy despite all patients being younger than 50 years at evaluation (median age, 41 years).⁸

Elevations of additional laboratory markers of inflammation and endothelial dysfunction have also been detected in patients with GCTs acutely and during long-term follow-up after chemotherapy. In a study of patients with GCTs who completed cisplatin-based chemotherapy within the prior 3 months, significantly increased levels of von Willebrand factor were detected.²⁷ With longer follow-up (median 7 years posttreatment), increased levels of fibrinogen, tissue-type plasminogen activator, and high-sensitivity C-reactive protein were also observed in chemotherapy-treated patients with GCTs compared with age-matched controls.²⁰ Finally, a recent report showed an increase in circulating endothelial cells (from endothelial injury) among GCT survivors (> 2 years from diagnosis) who had received chemotherapy compared with those who were chemotherapy-naïve.²⁸ These findings suggest the acute onset and persistence of endothelial dysfunction related to chemotherapy.

Carotid intimal medial thickness (IMT) has been found to correlate with increased risk of cerebrovascular accidents and myocardial infarctions in patients without known coronary artery disease.²⁹ The carotid IMT increased significantly over a 3.5-month course of cisplatin-based chemotherapy in patients with GCTs compared with the annual change in IMT in the general population.²⁷ Whether this finding is relevant to long-term GCT survivors is not yet clear, but lends further support to the hypothesis that direct vascular injury plays a role in long-term cardiac toxicity.

What is intriguing is that even in patients treated with orchiectomy alone, some markers of endothelial function seem to be abnormal relative to controls.²⁰ This suggests that chemotherapy may not be the sole etiologic insult responsible for the early onset and increased incidence of cardiovascular disease in this population, but that multiple pathways and factors likely contribute to therapy-related vascular injury. These may include an inflammatory response with cytokine release, oxidative damage, hormonal imbalances, metabolic disturbances, changes in electrolytes, and platelet aggregation. For example, cisplatin injection into the umbilical vein causes marked elevations of interleukin (IL)-1 and IL-6, and cisplatin-induced nephrotoxicity increases tumor necrosis factor (TNF)- α levels, leading to upregulation of additional cytokines, such as TNF- β , IL-1 β , RANTES (regulated upon activation, normal T-cell expressed and secreted), macrophage inflammatory protein 2 (MIP-2), monocyte chemoattractant protein 1 (MCP-1), and T-cell activation gene 3 (TCA-3).³⁰ Cisplatin may also cause an increase in reactive oxygen species, leading to nuclear factor kappa-B secretion and a proinflammatory response that results in mitochondrial dysfunction.³¹ Platelet aggregation in response to cisplatin has also been proposed to explain the increased incidence of myocardial infarction and cerebrovascular thrombotic events in young patients with no other vascular disease risk factors.³² Finally, cisplatin might also induce vascular injury through causing hypomagnesemia, leading to vasospasm.^{33–35}

Induction of Cardiac Risk Factors (Indirect Hypothesis)

Multiple studies have suggested an increased frequency of cardiovascular disease risk factors in patients treated for GCTs, supporting an alternative,

more-indirect explanation for the increase in vascular events in chemotherapy treated GCT survivors. Select studies are reviewed in Table 2.^{8,9,12,18,20,36–38}

Hyperlipidemia has been reported in up to 80% of chemotherapy-treated GCT survivors, although a wide range has been observed (32%–82%), with methodology and definitions varying by study.^{4,8} In a study of 62 patients treated with chemotherapy who, at evaluation, were younger than 50 years and at a median of 14 years posttreatment, 79% had elevated cholesterol, 35% had low high-density lipoprotein (HDL), and 25% had elevated triglycerides. All of these values were significantly abnormal compared with controls treated with orchiectomy alone.⁸ An observational study of 32 chemotherapy-treated survivors who were a median of 15 years posttreatment reported similar concerning results; 81% were found to have elevated total cholesterol, 15% had low HDL, and 44% had elevated triglycerides.¹⁸

The prevalence of hypertension is similarly increased in patients with GCTs who have received prior chemotherapy, including in 25% of patients in the observational study just mentioned.^{18,38} A large-scale study corroborated these findings.³⁸ In 1289 GCT survivors, the prevalence of hypertension was greater in patients treated with cisplatin compared with those treated with surgery alone, and the rates increased with higher cumulative cisplatin doses (39% with surgery alone vs. 50% with cisplatin of ≤ 850 mg, vs. 54% with cisplatin of > 850 mg; $P < .001$).³⁸ These findings remained significant after adjusting for testosterone levels and body mass index (BMI). Obesity has also been reported as increased in GCT survivors treated with chemotherapy. With a cutoff BMI of 25 or more, the previously mentioned study found 48% of GCT survivors who previously received cisplatin-based therapy were obese at a median of 15 years posttreatment.¹⁸ Like hypertension, this finding may also correlate with the cumulative dose of cisplatin administered. For instance, Sagstuen et al.³⁸ observed an increased prevalence of BMI of 30 or greater in patients with GCTs who received greater than 850 mg of cisplatin compared with patients treated with surgery alone (odds ratio [OR], 2.4; 95% CI, 1.3–4.4). In contrast, patients treated with lower doses of cisplatin had only a nonsignificant trend toward an increased prevalence of obesity compared with patients treated with surgery only.

Chemotherapy-Induced Cardiovascular Toxicity

Table 2 Prevalence of Cardiovascular Disease Risk Factors in Chemotherapy-Treated Patients in Select Studies Since 2000

Author (Year)	N ^a	Treatment Dates	Median Length of Follow-Up (Range)	Median Age at Follow-Up (Range)	Control Group (N)	Prevalence of Cardiovascular Risk Factors vs. Controls ^b (%)					Metabolic Syndrome (Definition)
						HTN (Definition)	Increased Lipids ^c (Definition)	DM (Definition)	Obesity (Definition)		
Meinardi et al. ⁸ (2000)	62	Before 1987	14 y (10–20 y)	42 y (30–50 y)	Stage I (40)	39 vs. 13 (SBP > 150 mm Hg, DBP > 95 mm Hg)	79 vs. 53 (TC ≥ 201 mg/dL)	NA	21 vs. 28 ^d (BMI > 27.8)	NA	
Strumberg et al. ¹⁸ (2002)	32	1977–1981	15 y (13–17 y)	40 y (30–59 y)	None	25 vs. NA (DBP > 95 mm Hg)	81 vs. NA (TC > 200 mg/dL)	NA	48 vs. NA (BMI ≥ 25)	NA	
Huddart et al. ⁹ (2003)	390	1982–1992	10 y (0–20 y)	41 y (23–72 y)	Stage I GCT (242)	13 vs. 9 ^d (antihypertension medication)	1 vs. 2 ^d (lipid-lowering medication)	NA	NA	NA	
Nuver et al. ²⁰ (2004)	90	1988–1999	7 y (NA)	37 y (20–65 y)	Stage I (44) and healthy patients (47)	22 vs. 23 vs. 11 ^d (SBP ≥ 135 mm Hg, DBP ≥ 85 mm Hg)	71 vs. 59 vs. 45 ^e (LDL > 131 mg/dL)	NA	22 vs. 27 vs. 11 ^e (BMI ≥ 30)	NA	
Nuver et al. ³⁷ (2005)	86	1988–1999	7 y (3–13 y)	37 y (20–65 y)	Stage I (44) and healthy patients (47)	NA	NA	NA	NA	26 vs. 36 vs. 9 ^e (≥ 3 factors per NCEP definition ⁴⁰)	
Sagstuen et al. ³⁸ (2005)	500	1980–1994	11 y (4–22 y)	44 y (23–75 y)	Surgery-only ^f (242) ^g	50 vs. 39 (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or antihypertension medication)	NA	NA	18 vs. 13 ^h (BMI ≥ 30)	NA	
Haugnes et al. ³⁶ (2007)	464	1980–1994	11 y (5–22 y)	43 y (15–52 y)	Surgery-only ^f (225) and healthy population (1150)	45 vs. 34 vs. 50 ⁱ (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or antihypertension medication)	68 vs. 67 vs. 84 ^d (TC ≥ 201 mg/dL)	3 vs. 2 vs. 3 ^d (by patient self-report)	18 vs. 13 vs. 21 ^d (BMI ≥ 30)	9 vs. 7 vs. 15 ^h (≥ 3 factors per NCEP definition ⁴⁰)	
Haugnes et al. ¹² (2010)	364	1980–1994	19 y (13–28 y)	49 y (31–69 y)	Surgery-only ^f (206) and healthy population (990)	26 vs. 12 vs. 13 (antihypertension medication)	14 vs. 14 vs. 9 ^e (lipid-lowering medication)	5 vs. 4 vs. 4 ^d (by patient self-report or fasting glucose ≥ 198 mg/dL)	17 vs. 19 vs. 23 ^d (BMI ≥ 30)	NA	

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; GCT, germ cell tumor; HTN, hypertension; LDL, low-density lipoprotein; NA, not available; NCEP, National Cholesterol Education Program; SBP, systolic blood pressure; TC, total cholesterol.

^aN varies slightly for individual factors due to missing data in papers for some variables.

^bDefinitions of individual factors vary by study. Comparisons of chemotherapy group to controls significant unless otherwise stated; percentages vary slightly due to missing data for individual factors.

^cCholesterol and fasting glucose values in definitions were converted from mmol/L to mg/dL where necessary for uniformity.

^dNot significant.

^eSignificant vs. healthy population controls but not vs. surgery patients.

^fIncludes both orchiectomy and primary retroperitoneal lymph node dissection patients.

^gA healthy population control group was also included in this study but prevalence rates of cardiovascular risk factors were not reported for this control group, and therefore these data are not included in the table.

^hSignificant only for patients who received > 850 mg of cisplatin.

ⁱSignificant vs. surgery patients but not vs. healthy controls.

The metabolic syndrome was recently recognized as an important cardiovascular disease risk factor.³⁹ Using a modified definition, the metabolic syndrome was reported in up to 40% of chemotherapy-treated GCT survivors younger than 60 years at a median of 11 years posttreatment.³⁶ This rate was significantly higher than that for survivors treated with surgery alone, with the greatest risk incurred by those treated with more than 850 mg of cisplatin (OR, 2.8; 95% CI, 1.6–4.7).³⁶ In a smaller study that used the conventional National Cholesterol Education Program Adult Treatment Panel III definition of the metabolic syndrome,⁴⁰ its prevalence was increased among a combined group of patients with stage I testicular cancer and chemotherapy-treated survivors compared with controls (chemotherapy-treated, 36% vs. stage I, 25% vs. controls, 9%; $P = .002$).³⁷ However, differences in metabolic syndrome rates were not significantly different between chemotherapy-treated patients and those managed with orchiectomy alone ($P = .232$).³⁷

These studies suggest that the prevalence of major cardiac risk factors in these GCT survivors exceeds those of the general population (Table 2). Several of these comorbidities, particularly the metabolic syndrome, have been linked to testosterone deficiency, providing a possible association with testicular cancer treatment.³⁷ However, most patients developing these risk factors have normal serum testosterone levels.³⁶ Independent of the metabolic syndrome, decreased testosterone levels can lead to endothelial dysfunction, impaired vascular smooth muscle reactivity, increased intima and media thickness of vessels, and increased synthesis of proinflammatory cytokines, as extensively reviewed by Traish et al.⁴¹ These pathologic changes offer an additional explanation for the associations between testosterone deficiency and cardiovascular events.

Recommendations

Regardless of the mechanisms contributing to the increased cardiac morbidity and mortality in this population, awareness of the increased risk offers a prime opportunity for intervention and prevention of late cardiovascular disease. Cardiac workup (e.g., referral to cardiology, electrocardiogram) in these patients should be based on clinical presentation, with an appreciation of their increased risk. With respect to cardiac risk factors, the differences in definitions, varia-

tions in patient populations (including prior treatment intensity and regimen), and wide ranges of prevalence rates across the available studies (Table 2) and uncertainty regarding the extent those prevalence rates are increased relative to the general population make it difficult to offer informed screening recommendations beyond the accepted guidelines for primary prevention of heart disease, although these have been suggested.⁴² Research is urgently needed to better define the prevalence of major cardiac risk factors in these GCT survivors as a first step toward recommending heightened screening and earlier intervention.

In the interim, until these data are available, patients undergoing treatment should be made aware of their future risk for these comorbidities and encouraged to establish care with an internist familiar with their increased likelihood of developing cardiovascular disease. Lifestyle changes should be highly encouraged. Patients should be given recommendations for adopting a heart-healthy diet and regular exercise as per the American Heart Association guidelines and, if necessary, to lose weight to achieve a goal BMI less than 25. Referral to a smoking cessation program (if applicable) is also critical, because up to 40% of patients with GCTs who were smokers at diagnosis may continue smoking for many years after treatment.⁴³ In addition, early institution of medications to more tightly regulate lipids and blood pressure may be beneficial. Primary prevention of coronary artery disease with aspirin should be considered in the context of each patient's risk. Administration of testosterone replacement to hypogonadal patients, particularly those with the metabolic syndrome, should also be considered.

Studies testing interventions are also greatly needed to provide evidence-based guidelines specifically addressing the increased cardiovascular risk in GCT survivors. In addition, physicians should have a low threshold for assessing GCT survivors with symptoms of angina for coronary artery disease or an acute coronary syndrome, regardless of age. Genetic factors, such as polymorphisms in the androgen receptor gene, leptin receptor gene, 9p21 (for coronary artery disease), or genes increasing the risks of diabetes and hyperlipidemia, may help determine which patients will develop cardiovascular disease with treatment. Further understanding of the role of genetics may allow for interventions specifically targeting GCT survivors at highest risk.

Conclusions

Surviving cancer, particularly metastatic disease, is an enormous accomplishment that requires courage, perseverance, quality medical care, a good support system, and even luck. It is concerning that the survival benefit of modern treatment of GCTs may be compromised by the consequences of treatment, particularly cardiovascular morbidity. Efforts are needed to better understand the mechanisms of treatment-related cardiac toxicities so that preventive and therapeutic interventions can be instituted. Since 1981, GCTs have been regarded as “a model for the curable cancer,”³ with the paradigms for their treatment extrapolated to the management of other neoplasms. Now, GCTs are again poised to help advance oncologic care, but this time in understanding and improving cancer survivorship. In doing so, GCTs have the opportunity to serve not only as “a model for the curable cancer” but also as “a model for the cured patient.”

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Feldman et al.

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