Prognostic factors in children with extracranial malignant germ cell tumors: a monocentric pediatric Tunisian study

Facteurs pronostiques des tumeurs germinales extracrâniennes de l'enfant : étude monocentrique pédiatrique Tunisienne

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RÉSUMÉ

Pré-requis: Les tumeurs germinales malignes représentent un groupe rare et hétérogène de cancers pédiatriques hautement curables.

But: L'objectif de notre analyse est d'étudier la prise en charge, le pronostic et les facteurs pouvant influencer la survie globale (SG) dans une unité d'oncologie pédiatrique Tunisienne.

Méthodes: Il s'agit d'une étude rétrospective ayant colligé entre Janvier 1998 et Décembre 2012 toutes les tumeurs germinales extracrâniennes traitées selon le protocole TGM95 de la SFOP (Société Française d'Oncologie Pédiatrique) dans une unité d'oncologie pédiatrique Tunisienne.

Résultats: L'âge médian des patients était de 57 mois (extrêmes: 1 jour, 13 ans). Nous avons colligé 19 filles et 14 garçons. Les tumeurs siégeaient dans la région sacrococcygienne dans 12 cas, les ovaires dans 11 cas, les testicules dans 6 cas, la région rétropéritonéale dans 3 cas et le médiastin dans 1 cas. Après un recul médian de 26,1 mois (extrêmes: 0-96 mois), la SG à 2 et 5ans était respectivement de 82% et 75%. La survie sans événements était de 79% à 2 ans et 74% à 5 ans. Plusieurs facteurs pronostiques ont été étudiés selon la méthode Kaplan-Meier. L'analyse univariée a montré que les facteurs qui influençaient significativement la SG étaient le stade (p=0,04), la qualité de l'exérèse (p<0,001) et la rechute (p=0,0001). L'étude multivariée a montré que seuls la qualité de l'exérèse et le stade clinique étaient significatifs pour la SG à 5 ans.

Conclusion: Le stade de la maladie, la qualité de l'exérèse et la rechute sont les facteurs pronostiques les plus significatifs dans notre étude pour la SG. L'amélioration de la survie des patients porteurs de tumeurs germinales extracrâniennes est un véritable défi essentiellement dû au succès des traitements de rattrapage.

Mots-clés

Tumeurs germinales; enfant; pronostic.

SUMMARY

Background: Extracranial Germ cell tumors (GCT) are a rare and a heterogeneous group of pediatric cancers but highly curable.

Aim: We aimed to review management, outcome and prognostic factors that influence overall survival (OS) in a pediatric Tunisian oncologic unit.

Methods: We retrospectively evaluated between January 1998 and December 2012, 33 patients affected by extracranial germ cell tumors and treated according to TGM95 protocol established by the SFOPin a pediatric Tunisian oncologic unit.

Results: Patients had a mean age of 57 months (ranges: 1 day-13 years). There were 19 girls and 14 boys. Primary sites included 12 sacrococcygeal, 11 ovarian, 6 testicular, 3retro peritoneal and 1 mediastinal site. After a mean follow up of 26.1 months (ranges: 0-96 months), OSat 2 years and 5 years were respectively 82% and 75%. Event-free survival were respectively 79% at 2 years and 74% at 5 years. Various prognostic factors have been studied according to Kaplan-Meier. Univariate analyses identified significant factors which influence strongly OS: the stage (p=0.04), the completeness of surgery (p<0.001) and the relapse (p = 0, 0001). A multivariate study showed that only the quality of resection and the clinical stage remained strong significant prognostic factors (p=0,021) for 5-year OS.

Conclusion: Disease stage, completeness of surgery and relapse have been established as the most powerful prognostic parameter in our analysis. The improvement of survival of patients affected by extracranial germ cell tumors in Tunisia is a real achievement mainly due to the success of salvage treatments.

Key-words

Germ cell tumors; children; prognosis.

Germ cell tumors (GCT) are a rare and a heterogeneous group of pediatric cancers regarding histology, clinical manifestations and evolution. It accounts for 3% of all pediatric cancers (1). Extracranial localizations represent 60 to 82%of all GCT. Before the introduction of effective chemotherapy and particularly cisplatin regimen, 3-year survival rate of children with extracranial malignant didn't exceed 15% to 20% with surgery and radiation therapy (2). The use of platinum-based chemotherapy in the past 2 decades improved dramatically the prognosis for GCTand allows sufficient systemic tumor control since 5-year survival rates exceed 90% (3). This is why, appropriate treatment should be adapted to prognostic factors in order to improve long-term survival while minimizing treatment-related long-term sequela. In 1997, the largest data collection involving 10 countries with several thousands of patients presenting nonseminomatous germ cell tumors, identified as independent adverse factors, mediastinal primary site, presence of non-pulmonary visceral metastases such as liver, bone, brain and the degree of elevation of AFP (alfa fetoprotein), βHCG (beta human chorionic) and lactate dehydrogenase. For seminoma, the predominant adverse feature was the presence of non-pulmonary visceral metastases (3).

The aim of this study is to identify risk factors which influence prognosis in GCT among a Tunisian series of 33 pediatric cases.

METHODS

Patients

Between January 1998 and December 2012, we retrospectively evaluated 33 children affected by an extra cranial germ cell tumor. Eligibility requirements for the study included age under 18 years and lack of prior therapy.Patients with the following subtypes of germ cell tumor were included: germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, mature or immature teratoma.

Investigation and staging

A determination of tumor markers, AFP and βHCG was done prior to the starting of treatment with the same Kits in the same laboratory throughout the treatmentand before each course thereafter. Diagnosis was established by raised serum AFP orHCG levels, or by histologic prove (biopsiesor surgical resection).Medical evaluation included personal and family history, medical history, physical examination, complete blood count,tumor markers and creatinine. Diagnostic imaging evaluation included ultrasound exam, Computerized Tomography +/- Magnetic Resonance Imagingof the chest or the abdomen. An extension imaging was performed including chest X ray +/-thoracic Computerized Tomography for all patients, Technetium bone scintigraphy in case of sacrococcygeal tumors and abdominal Computerized Tomography in case of testicular tumors.

Treatment

Patients were treated according to TGM95 protocol established by the SFOP (French Society of Pediatric Oncology). The therapeutic strategy depends on the initial extension of disease, the post-operative stage (according to TNM classification), the level of secretion of tumor markers (AFP higher or lower than 15.000 ng/ml) and histological components. Patients having secretary tumors were classified into three groups: low-risk group (initial AFP < 15.000ng/ml, localized and operable tumor at diagnosis) in which there is no indication to preoperative chemotherapy, standard risk group (initial AFP < 15.000ng/ml, no metastases) in which patients receive an alternation of VBP courses, and high-risk group (**AFP ≥ 15.000** ng/ml and/or metastases) in which patients receive an alternation of VIP courses. The number of courses depends on decrease of markers levels: patients received two additional courses after normalization of their AFP levels with a minimum of three and a maximum of six courses. Courses were given every 3 weeks after hematologic recovery. VBP course consists of vinblastine3mg/m² day 1 and 2, Bleomycin15 mg/m² day 1 and 2, Cisplatin 100mg/m² day 3. VIP course consists of VP16 75mg/m² from day 1 to day 5, Ifosfamide 3 g/m² day 1 and 2 and Cisplatin 10 mg/m² from day 1 to 5. It was considered that remission was likely when AFP/HCG levels had returned to normal, and imaging confirmed remission or showed considerable reduction in the size of the tumor. This chemotherapy was followed by surgical removal of the tumor residuum in all cases.

Statistical analysis

Event free survival (EFS) and Overall survival (OS) rates were expressed using Kaplan-Meier analysis. Overall survival was defined as the time from study entry until death or last reported contact and event free survival was determinate as the time from study entry until occurrence of disease progression or relapse. The log-rank test was used to assess the statistical significance of possible prognostic factors such as age, stage, primary site, AFP level (<15.000 versus **≥15.000**), metastases, prognostic group, completeness of surgery and relapse. **A multivariate study has been realized by analyzing factors 2 by 2**. A test was considered significant when p was less than or equal to the threshold of 0.05.

RESULTS

Patients had a mean age of 57 months (ranges: 1 day-13 years) with a frequency peak before 2 years (n=12/33). There were 19 girls and 14 boys. Primary sites included 12 sacrococcygeal (36.3%), 11 ovarian (33.3%),6 Testicular (18.2%), 3retro peritoneal (9.1%) and 1

mediastinal (3%) site. 16 patients (48.5%) had high rates of AFP with an average rate of 18470ng/ml and a median rate of 9470ng/ml (ranges: 150-60570 ng/ml). Only 2 patients had high levels of βHCG (236 and 669MUI/ml). Among the 16 secretary tumors, 9 patients (56.25%) were classified in the high risk group, 4 patients (25%) in the standard risk group and only 3 patients (18.75%) in the low risk. The stage distribution according to TNM classification included 15 stages I/II (45%), 15 stages III (45%), and 3 stages IV (9%).ThZclinical and laboratory characteristics of patients are resumed in table 1.

Table 1 : Clinical and laboratory characteristics of patients

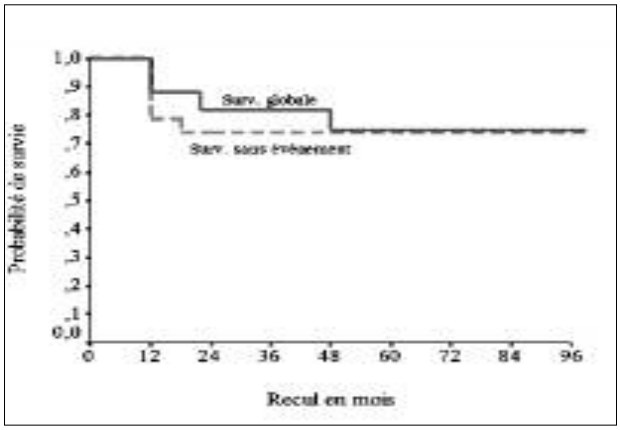
characteristic	Number of patients	%
Sexe		
male	14	42
female	19	58
Stage		
i/ii	15	45
iii	15	45
iv	3	9
Primary sites		
Sacrococcygeal	12	36
Ovarian	11	33
Testicular	6	18
Retroperitoneal	3	9
Mediastinal	1	3
Histology		
secretary tumors	16	48
no secretary tumors	17	51
AFP level (16 secretary)		
<15.000	10	60
≥15.000	6	40

Histologically, sacrococcygeal tumors were for the majority mixed tumors composed particularly bythe association of a mature or immature component and a yolk sac component. We noted in ovarian tumors the predominance of malignant tumors (2 dysgerminoma, 3 mixed tumors,and 2 yolk sac tumors) compared to mature teratoma (4). Among testiculartumors,we enumerated 2 yolk sac tumors, 2 mixed tumors, 1 embryonal carcinoma and animmature teratoma. In retro peritoneal tumors,we reported 2 mature teratomas and animmature teratoma. The only mediastinal tumor was a yolk sac tumor.

After a mean follow up of 26.1 months (ranges: 0-96 months), overall survival at 2 years and 5 years were respectively 82% and 75%. Event-free survival were respectively 79% at 2 years and 74% at 5 years (figure.1).We reported in this analysis 6 deaths (18.2%) caused by chemotherapy toxicity in one case, by tumoral progression in 3 cases and by metastatic relapse in spite of second line chemotherapy in 2 cases.

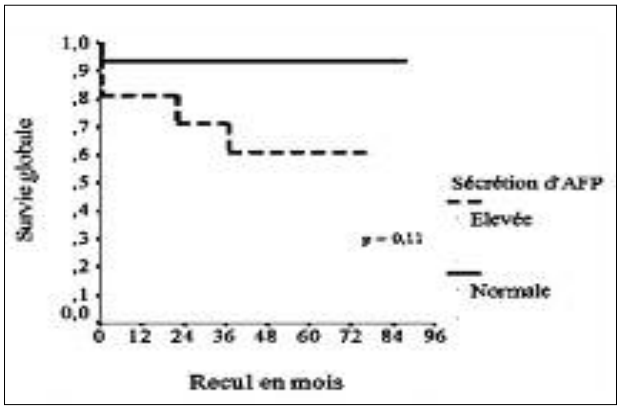
Various prognostic factors have been studied. As a first approach, age doesn't seem to influence prognosis significantly. Besides, 5-year- OS doesn't differ significantly according to site: 78% for sacrococcygeal tumors, 82% for ovarian tumors, 83% for testicular sites and 100% for retroperitoneal ones (p= 0,11). The only patient affected by mediastinal tumors died by tumoral progression.

Figure 1: Overall survival and event free survival



Metastases were also without significance for 5-year overall survival: 100% for metastatic forms (3 patients) and 70% for localized forms (33 patients) (p=0,44). Secretion of AFP was of borderline significance for reduced OS in secretary tumors compared to no secretary tumors (61% versus 94%,p = 0.11) (figure 2).

Figure 2: Kaplan-Meier survival curves of overall survival rates by secretion of AFP (P=0,11)



Furthermore, OS did not statistically differ significantly by rate of AFP (67% if AFP rate<15.000 versus 70% if **AFP rate ≥15.000)** (p=0,44). 5-year OS was better in patients of the low risk group (100%), compared to standard risk group and high risk group witch survival was only 59%, but this factor has no significant value (p = 0.32).Moreover, univariate analyses identified stages 1

and 2 as having statistically significantly better OS than stage 3 or 4 (100% versus 62%, p = 0. 04) (figure.3).On the other hand, 5-year OS was significantly better in cases where resection was complete (92%) compared to those who have underdone no or incomplete surgery (22%)(p<0.001) (figure 4).Classical multivariate methods identified relapse as the most important prognostic variable since 5-yearOS was 75% in patients who did not relapse compared to 25% in those who presented at least onerelapse. (p = 0, 0001) (figure 5).

Figure 3: Kaplan-Meier survival curves of overall survival rates by stage (stage 1+2 versus 3+4, P=0,04)

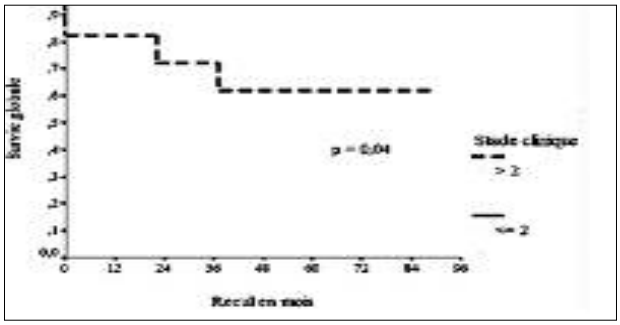


Figure 4: Kaplan-Meier survival curves of overall survival rates by quality of chirurgical resection (P<0,001)

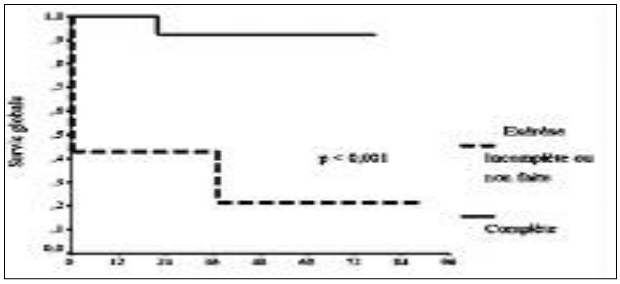
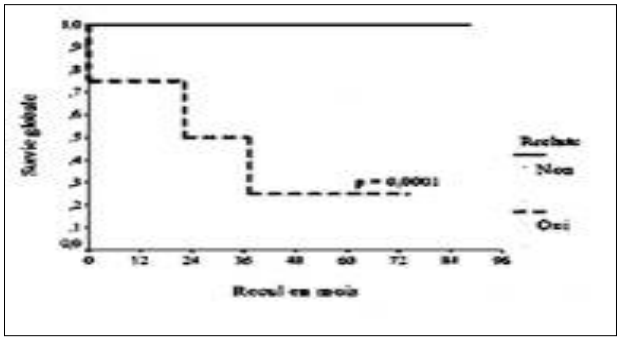


Figure 5: Kaplan-Meier survival curves of overall survival rates by relapse (p=0,0001).



A multivariate studyshowed by analyzing factors 2 by 2 that only the completeness of resection and the clinical stage remainedstrong significant prognostic factors (p=0,021). All prognostic factors are resumed in table 2.

Table 2 : Prognostic variables influencing 5-year Overall Survival

variable	Number of patients	5-Year Overall survival	p
Primary site			
-Retroperitoneal	3	100%	0,11
-Testicular	6	83%	
-Ovarian	11	82%	
-sacrococcygeal	12	78%	
Extent of disease			
I-II	15	100%	0,04
III-IV	18	62%	
AFP Secretion			
Yes	16	61%	0,11
No	17	94%	
AFP Secretion			
<15.000	10	70%	0,44
≥15.000	6	67%	
Metastases			
Yes	3	100%	0,44
No	30	70%	
Risk group secretary tumors			
Low risk intermediate/high risk	3	100%	0,32
Resectability (tumor totally removed)	13	59%	
Yes	7	92%	0,001
No	14	22%	
Relapse			
Yes	4	25%	0.0001
No	29	100%	

DISCUSSION

Prospective multicenter protocols for germ cell tumors in children and adolescent were performed in several countries such as the United States and European countries. Prognosis of extracranial GCT depends on histology, age, stage of disease, primary site and serum markers level (2).We noted in our study a high proportion of patients with advanced disease (stage III: 45%, stage IV: 9,1%), which indicates that in our country, delay of recognition of symptoms may result in delayed referral to specific oncologic units. This conclusion has been also reported by other series like the GCT-91 study elaborated by the Brazilian Pediatric Oncology Society (4).

To our knowledge, this is the first Tunisian series published concerning germ cell tumors in childhood and adolescent.

In our study, some factors did not influence OS: Age, site, metastases, rate of AFP and prognostic group. Secretion of AFP was of borderline significance for reduced OS.

Moreover, univariate analysis identified significant factors, which influence strongly OS: the stage, the completeness of surgery and the relapse.

Age does not influence prognosis in our study which was consistent with Backer and al (5). However, other studies showed that age influence not only the clinical presentation, but also the outcome of GCT tumors. In fact, Isaacs reported that fetuses with teratomas detected antenatally, have 3 times the mortality rate compared with postnatally diagnosed neonates (6). It is due to complications caused by tumors (cardiac failure in case of voluminous tumors, airway compression by mediastinal tumors and postoperative hemorrhagic and infectious complications). Mann and al. noted also that 5-year OS in newborn was worse than in other ages (86,9% for newborn versus 100% for others) (p=0,031) (7). On the other hand, univariate analysis in Marina and al. (8) study identified age>12years as a highly significant prognostic factor for 5-year EFS (48.9% versus 84.1%; p <0.0001) and for 5-year OS (53.7% versus 88.5%; p<0.0001(8). Multivariate Cox proportional hazards regression identified only age >12 years as a significant prognostic factor for EFS (P<0.0002). In multivariate Cox regression for OS, the combination of age and primary site was highly significant (P <0.0001).

In our study, 5-year OS was the best among patients affected by testicular and retroperitoneal tumors but this difference was not significant (0,11). Mediastinal localizations have often a poor prognosis and elsewhere are immediately treated as high risk tumors. Backer and al (5), noted that mortality rate was 28.6% for Mediastinal tumors and 37.5% for cervical tumors, while it was 3%, 5%, 8% 8.6% respectively for ovarian, testicular, retroperitoneal and sacrococcygeal tumors (5). The study performed by Bilmire (9) about 36 cases of mediastinal tumors noted an OS and EFS of 71 and 69% (9). These lower rates are essentially due to the surgical difficulties. The author concluded that aggressive attempt at complete tumor resection, should be done in all patients having mediastinal tumors even if Bulky tumors persists after induction chemotherapy.In the United Kingdom, between January 1989 and December 1997, 192 children with malignant extracranial GCT were registered (10). Stage I testicular and some ovarian GCT were resected and monitored with AFP («watch-and-wait» approach). Patients with recurrent stage I disease and all other patients received JEB (etoposide 120 mg/m^2 on days 1 through 3, carboplatin 600 mg/m^2 on day 2, and bleomycin 15 mg/m^2 on day 3). The 5-year OS rate in 1999 was 93.2%. Site had prognostic significance.

Completeness of surgery was a significant factor for 5-year OS in our analysis. This factor has also been reported by several studies (2). TGM 95 included partly 19% patients with malignant refractory or recurrent GCT (11). After treatment combining surgery and chemotherapy (high dose chemotherapy in 10 cases), the 5-year EFS and OS were of 26% and 32% respectively. The quality of surgery was, like in our study, a strong significant factor influencing EFS (p=0,0003), confirming thus that complete excision of tumor is essential in GCT.

Stage influences strongly prognosis in our study, which was consistent with literature (12) and particularly with Mann study in UK (6) who noted better OS and EFS in localized stages (I-II) compared to advanced stages (III-IV): respectively 98% versus 96% (p=0,028) and 95% versus 78% (p=0,04).

Metastases were no significant in our study because of the small number of patients (3 metastatic /33patients).Between 1983 and 1995, 71 patients with malignant sacrococcygeal GCT were prospectively enrolled onto the German cooperative protocols MAKEI 83/86 and 89 for non-testicular GCT (13). Metastases at diagnosis were significant prognostic predictor. In fact, patients with locally advanced and metastatic tumors had better prognosis with neoadjuvant treatment (5-year OS =83% with neoadjuvant chemotherapy versus 45% without chemotherapy, p =0.01). Authors concluded that sacrococcygeal GCT can be successfully treated with up-front cisplatinum-based chemotherapy followed by delayed but complete tumor resection even in case of metastatic tumors. Later, in the German trial (MAKEI 89) concerning sacrococcygeal tumors, visceral metastases influence strongly prognosis whereas bone extension doesn't; 5-year OS was however good in case of metastases tumors (71% versus 82%) which is due to the efficacy of cisplatin in these forms (14).

In our study, there was no significant difference between all histologic types. However, it was recognized as an important significant factor in many studies. Mann and al. (7) noted significantly better OS and EFS in mature teratomas compared to immature teratomas (respectively 5-year OS= 99% versus 95%, 5year EFS=92% versus 85 with a significant difference (p=0,034 for OS and 0,0196 for EFS)). Mann (7) reported also the greater risk of recurrence for sacrococcygeal than ovarian or testicular tumors and the importance of complete resection. However, close oncological follow-up is carefully recommended for all patients with particularly sacrococcgeal teratoma (with markers monitoring) in order to permit early diagnosis and treatment of yolk sac tumor recurrence (7). French studies (12) reported also good prognosis of ovarian dysgerminoma like in our series (5-year OS=100%, 5 year EFS=97%). According to Backer (5), patients with choriocarcinoma, embryonal carcinoma, immature teratoma, yolk sac tumor and mixed GCT had a lower probability of EFS than patients with mature teratoma or gonadoblastoma (p < 0.001).

Our analysis revealed that relapse was the most prognostic factor (p = 0. 0001). The prognosis decreased also dramatically with the number of relapses. Thus, the 5-year-OS reached in our analysis 74% in case of complete remission after the first relapse but equals only

10% in case of second or third relapse. Before the introduction of chemotherapy, especially Platinum regimen, relapses were frequent and often fatal. The German study (MAKEI 83/86 and 89) including 22 cases of relapsed sacrococcygeal germ cell tumors (13) reported very low OS rate (42%) and 5 years- EFS rate (30%). Better results have been published by De Giorgi which stipulates that the 2 year OS for first relapsing patients was 78% compared to second or third relapsing patients (43%); high dose chemotherapy induces a high rate of long-term remissions even as third-line treatment. Moreover, the author concluded that salvage high dose chemotherapy should be investigated in prospective trials (15).

After studying all factors 2 by 2 in our series, the strongest significant factors were stage and quality of surgery. In multivariable analysis of 519 patients with GCTs conducted by the Children's Oncology Group (United States) or the Children's Cancer and Leukemia Group (United Kingdom) between 1985 and 2009, stage IV disease (P =0 .001), age ≥ 11 years (P < 0.001), and tumor site (P < 0.001) were significant predictors of worse long-term disease-free survival. Elevated Alpha-fetoprotein (AFP) ≥ 10,000 ng/mL was associated with worse outcome, whereas pure yolk sac tumor (YST) was associated with better outcome (16).

CONCLUSION

Disease stages, completeness of surgery and relapse have been established as the most powerful prognostic parameters in our analysis, superior to tumor marker levels or primary site of the tumor. Based on our experience, elaborating a prognostic factor-based staging classification is the best way to improve the prognosis of patients having GCT. Our analysis was limited because of the small number of patients available to study. This is why it is important to do a multicentric Tunisian study.

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