Recent advances in molecular biology and treatment strategies for intracranial germ cell tumors

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Background: **Intracranial germ cell tumors (IGCTs) are a group of rare pediatric brain tumors which include various subtypes. The current understanding of the etiology of the tumors and their optimal management strategies remain controversial.**

Data sources: **The data on IGCTs were collected from articles published in the past 20 years, and the origin and etiology of IGCTs at molecular level as well as the relative roles of varied treatment strategies in different prognosis groups according to Matsutani's classification were reviewed.**

Results: **Recent cellular and molecular evidence suggests that IGCTs may arise from the transformation of endogenous brain cells; and findings in the molecular characterization of IGCTs suggest roles of CCND2, RB1, and PRDM14 in the pathogenesis of IGCTs and identify the KIT/RAS and AKT1/mTOR pathways as potential therapeutic targets in future. According to Matsutani's classification of IGCTs, the good prognosis group includes both germinomas and mature teratomas. For germinomas, both radiation alone and reduced-dose radiotherapy in combination with adjuvant chemotherapy are effective, while complete surgical excision is recommended for mature teratomas. In the intermediate prognosis group, immature teratoma has been successfully treated with gamma knife surgery. However, for intermediate prognosis IGCTs other than immature teratomas, gross total resection with adjuvant chemotherapy and radiotherapy or gamma knife surgery may be necessary to achieve cure. In the poor prognosis group, survival outcomes are unsatisfactory, and complete surgical resection combined with more intensive chemotherapy and radiotherapy remains the best available treatment option at this time.**

Conclusions: **IGCTs should be strictly classified according to their pathological categories before administering pathology-specific treatments. Although open microsurgical excision is the traditional surgical strategy for IGCTs, recent publications also support the role of endoscopic surgical options for pineal region IGCTs.**

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Review article

Introduction

Intracranial germ cell tumors (IGCTs) are a group of rare pediatric brain tumors, compromising 5.4%-15.3% of primary central nervous system (CNS) tumors of childhood.[1-4] The overall male-to-female incidence ratio is about 4-5:1. A recent report showed that Japan and the United States share a similar incidence of primary germ cell tumors, exhibiting the same gender-based patterns.[5] Primary IGCTs are usually located either in the suprasellar or pineal regions.[6] According to the classification published by the WHO in 2007, the subtypes of these tumors include germinoma, teratoma (immature and mature teratomas, teratomas with malignant transformation), yolk sac tumor, embryonal carcinoma, choriocarcinoma, and mixed germ cell tumor. Alternatively, IGCTs can be divided into good, intermediate, and poor prognosis groups according to Matsutani's classification (Table).[7] Types of IGCTs are different significantly in geographical and gender distribution, histological composition and treatment outcomes. However, the roles of surgery, chemotherapy, radiotherapy, and gamma knife surgery in the treatment of patients with such lesions remain controversial. This study is to review all the reports in the past decades, with an emphasis on molecular changes, tumor management, and prognosis of different subtypes of IGCTs.

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Table. Therapeutic classification of intracranial germ cell tumors

Good prognosis group
Germinoma, pure
Mature teratoma
Intermediate prognosis group
Germinoma with syncytiotrophoblastic giant cells
Immature teratoma
Teratoma with malignant transformation
Mixed tumors mainly composed of germinoma or teratoma
Poor prognosis group
Choriocarcinoma
Yolk sac tumor
Embryonal carcinoma
Mixed tumors mainly composed of choriocarcinoma, yolk sac tumor, or embryonal carcinoma

Classification proposed by Matsutani, et al.[7]

Etiology and genetics of IGCTs

IGCTs are proposed to derive from the progenitors of the male and female germ cell line and are thought to derive from a progenitor cell from a distant organ that mismigrated and trapped in midline locations along the body's anteroposterior axis during early embryogenesis. The hypothesis is supported by the evidence that GCTs in the brain or other sites along the body's midline and gonadal GCTs share several common features, such as specific gene expression, DNA methylation, chromosomal alterations, and marker secretion.[8,9] In recent years, however, many studies reported teratoma, one subtype of GCT, can be generated from other non-progenitor germ cell.[10] More strikingly, Kim et al[11] in 2009 found that the overexpression of just a single gene, *Oct4*, was sufficient to turn neural stem cells into normal progenitor stem cells in the brain. This strongly support the hypothesis that teratoma could be derived from other cell types beyond germ cell progenitors in human body. Furthermore, evidence supports that the other subtypes of GCTs are "lineage-related" to teratoma. For example, GCTs are often found to be of mix histology containing four histological subtypes.[12-15] Each subtype of a GCT can reappear as a different subtype following resection.[16,17] This indicates that the cells of these tumors can give rise to different histological subtypes and therefore share a common cellular lineage. Hence, if teratoma could arise from non-germ cell lineages, then the same condition could exist in other subtypes of IGCTs.

Fluorescence *in situ* hybridization has demonstrated that amplification on chromosome 12p, particularly 12p13, occurrs in nearly all IGCTs, regardless of histological subtypes.[18,19] Losi et al[20] showed that a near-triploid complex karyotype (62 chromosomes), including two copies of isochromosome 12p, was found in a case of malignant mixed teratoma-embryonal carcinoma. This case suggested that the formation of isochromosome 12p may be associated with the development of malignant germ cell tumors. A further study demonstrated the aberrations of both *CCND2* (12p13) and *RB1* (13q14) gene as well as the gain of the *PRDM14* (8q13) gene in patients with IGCTs.[21] The aforementioned aberrations suggested the potential role of the Cyclin/CDK-RB-E2F pathway in the pathogenesis of intracranial GCTs, whereas frequent gain of *PRDM14* (8q13) indicates that transcriptional regulation of primordial germ cell specification is an important factor for the development of this tumor.[21] Moreover, *HOP/NECC1*, a gene located on human chromosome 4q11-q12, is a suppressor in choriocarcinogenesis and the loss of its expression is involved in malignant conversion of placental trophoblasts.[22]

GCTs, both intracranial and extracranial ones, demonstrate possible overexpression of the protooncogene c-kit, especially in the germinoma cells. In addition, cerebrospinal fluid (CSF) examination of patients with GCTs displayed a significantly higher level of s-kit (a soluble isoform of c-kit) in germinomas.[23] In 2014, Wang et al[24] reported the KIT/RAS signaling pathway frequently mutated in more than 50% of IGCTs in all the 62 cases. Copy number gains of the *AKT1* gene at 14q32.33 locus in 19% of patients is the novel somatic alterations in the AKT/mTOR pathway. Therefore, the inhibition of KIT/RAS activation and the AKT1/mTOR pathway is proposed as the potential promising therapeutic strategy. Expression of p53 protein in 94% and expression of p21 (WAF1/Cip1) in 20% of intracranial germ cell tumors are associated with decreased sensitivity to radiotherapy, chemotherapy, and poor prognosis.[25]

The good prognosis group: pure germinoma and mature teratomas

Radiotherapy

Germinomas are considered to be very radiosensitive tumors. Long-term follow-up demonstrated that radiotherapy could bring about complete clinical and radiographic recovery in patients with pure germinoma who are diagnosed via stereotactic biopsy.[26] The 10-year overall survival rate can reach up to 90%.[27,28]

Although radiation therapy is acknowledged to be an important part of treatment strategies for germinoma, opinions regarding optimal dosage and volume remain divergent. For patients with disseminated germinoma, craniospinal irradiation (CSI) remains the standard of care. Formerly, 36 Gy of CSI was administered with a boost to the primary lesion (s) to 50 Gy. However, more

and more studies recommend the reduction of dose in CSI for IGCTs patients in recent years. The German MAKEI 89 trial supported the reduction in CSI to 30 Gy with a boost to 45 Gy.[29,30] In 2013, the SIOP CNS GCT 96 trial reported a 98% event-free and overall survival with CSI dose of 24 Gy accompanied by a boost to 40 Gy.[31]

Current standard of care for localized germinoma in the United States is 21-24 Gy whole-ventricular irradiation (WVI) with a boost to the primary tumor site for a total of 40-45 Gy. In addition to involved-field radiation, whole-brain irradiation (WBI) or WVI should also be administered while considering the high rate of relapse within the ventricles outside the radiation field with involved-field radiation alone, to be the result of subarachnoid invasion by micrometastases.[32-34] However, spinal irradiation can be safely eliminated without significant risk for spinal relapse. In their analysis of 180 cases of germinoma, Shikama et al[35] reported that preventive whole spinal irradiation showed no benefit in terms of progression free survival. Haas-kogan et al[32] found that none of their 35 germinoma patients who received WBI followed by a boost to the primary tumor suffered spinal recurrence after irradiation with a mean follow-up time of 4.5 years.

It remains controversial whether irradiation therapy is effective for mature teratoma. Sano[36] and Ogawa et al[37] revealed the combination of surgery and radiotherapy had good curative effect on mature teratoma with a 10-year overall survival rate of up to 93%.[36] However, Selcuki et al[38] and Jakacki[39] argued that mature teratoma was not sensitive to radiotherapy, but could only cause brain trauma. They believed that mature teratoma is a potentially resectable, surgically curable tumor. Hence, the total removal of tumor is the treatment of choice. The prognosis in children with benign teratoma is very favorable after complete surgical excision as they reported.

Chemotherapy

Germinoma is sensitive to chemotherapy, which is platinum–based, combining with vincristine, etoposide, cyclophosphamide, bleomycin or methotrexate. Although multiple regimens have been shown to be effective, carboplatin and etoposide regiment was advocated by many experts to patients with diabetes insipidus due to its comparable efficacy and fewer complications when compared with ifosfamide and cisplatin-containing regimens.[40,41] However, chemotherapy in the absence of radiotherapy has been associated with an unacceptably high recurrence rate. Shibamoto et al[42] noted that although symptoms of germinoma disappeared in 90% of patients after receiving the regimen of platinum and etoposide or the regimen of bleomycin, platinum and etoposide for 6 cycles, 80% of recurrent cases developed within 3 years and 90% within 5 years. Kumabe et al[43] used the same regimens and reported 71.4% of tumors recurred at a mean period of 19 months after the initial therapy. The mean follow-up period was 53 months in this study. While radiotherapy cannot be eliminated completely, the addition of neoadjuvant chemotherapy has allowed the successful reduction in the dose and/or volume of radiation without compromising outcomes. Aoyama et al[44] reported the 5-year survival rate was 100% in 17 cases treated with a regimen of platinum and etoposide for 3-5 cycles followed by local field radiotherapy to a total dose of 24 Gy. Fouladi et al[45] reported there were similar effects of CSI on the regimen of carboplatin and etoposide chemotherapy (2-3 cycles) plus local field radiotherapy (total dose: 25-35 Gy) with a similar 5-year survival rate. Nguyen et al[46] reported the same 5-year survival rate of both CSI and chemotherapy followed by local field radiotherapy. However, this combined therapy was found to be co-related with spinal tumor recurrence. The rate of distant control in the spine at 5 years was 62% for patients who received focal irradiation and 100% for patients who received CSI (P=0.04).

Although beta-human chorionic gonadotropin (HCG)-secreting tumors were thought to be more likely to recur than their non-secreting counterparts, whether these tumors require more intensive chemotherapy regimens remains controversial. Subsequent studies[40,41] suggested that there was no difference in recurrence rates between patients whose CSF beta-HCG was negative or positive when they received at least whole-ventricle irradiation. Thus, the best treatment strategy remains a lack of consensus for patients with histologically proven germinoma accompanied by serum or CSF beta-HCG levels >50 IU/L.[40]

Open microsurgical excision

It is certain that surgery could provide therapeutic benefit for intracranial mature teratomas, and total tumor resection is recommended by numerous experts for the treatment of this type of benign tumor.[37] In contrast, surgery for germinoma has not been favored historically by neurosurgeons, although there are several arguments that support a role for surgical treatment in germinomas. Firstly, maximal tumor removal can allow for a more accurate histologic diagnosis than stereotactic biopsy, as many tumors which are thought to be pure germinomas may contain non-germinomatous elements due to sampling error, potentially leading to undertreatment and inferior outcome.[47] Secondly, experts previously opposed surgery because of the potential morbidity associated with procedures targeting the pineal region or other deep brain tissues. However, as neurosurgical techniques have evolved, the mortality and morbidity of surgical

treatment for this kind of tumor decline dramatically. Thirdly, an analysis of pooled data from the First, Second, and Third International CNS Germ Cell Study Groups found better outcomes in patients who had less than 1.5-2 cm residual disease, suggesting that more aggressive resection may provide some benefit.[47,48] Finally, only surgical treatment can realize intracranial decompression and reduced hydrocephalus.

The intermediate and poor prognosis groups

The intermediate and poor prognosis groups include embryonal carcinoma, endodermal sinus tumor (also called yolk sac tumor), choriocarcinoma, teratoma (including immature teratoma and teratoma with malignant transformation), and mixed germ cell tumor. Historically, these tumor subtypes were rarely identified. However, different patterns of recurrence and survival have been reported among these different subtypes.[49-51] Therefore, the relative roles of surgical resection, radiotherapy, chemotherapy, and gamma knife surgery in the management of patients with such lesions remain controversial.[52,53]

Microsurgical treatment

For tumors contain malignant histology, surgical treatment is effective and very important. Many experts suggest that when there is need for surgery, tumor resection is preferred rather than stereotactic biopsy unless the risk of surgical comorbidity is too high.[53-55] Schild et al[51] reported that patients who underwent subtotal resections or biopsies had significantly poorer survival rates than patients who underwent complete resection. The 3-year survival rate was 0% for patients who underwent biopsy alone and 32% for patients who underwent subtotal resection, compared with 73% for patients who underwent macroscopic total resection (P=0.0001). However, Calaminus et al[29] reported that complete or incomplete surgery had no significant effect on survival (P=0.12) in a series of 41 patients with malignant intracranial non-germinomatous GCTs. Huang et al[53] reported that there was no statistically significant correlation between total resection and survival (P=0.139) in the intermediate prognosis group with 39 cases of non-germinomatous IGCTs.

Radiotherapy

In comparison to germinoma, non-germinomatous IGCTs are much less radiosensitive. Treatment regimens utilizing irradiation without chemotherapy have historically resulted in a 5-year overall survival rate of only 20%-40%, and a median survival period of 18 months.[56] As Matsutani et al[56] reported, although initial reduction in tumor size and decrease in biomarkers were observed in 90% of patients after radiotherapy, 45% of these tumors recurred rapidly during the follow-up period. Ogawa et al[37] reported that among 32 patients, 5 patients who did not receive spinal irradiation developped spinal metastasis, and 6 who received spinal irradiation did not develop spinal metastasis.

Chemotherapy and chemotherapy-radiotherapy combination

The addition of neoadjuvant chemotherapy to radiation therapy has significantly improved the survival rate in patients with non-germinomatous IGCTs and is currently considered as the standard of care in the United States. With the treatment of germinoma, the chemotherapy regimens for non-germinomatous IGCTs are platinum-based. Multiple regimens including cisplatinum+vincristine+bleomycin, cisplatinum+etoposide/carboplatin+etoposide, and ifosfamide+carboplatin+etoposide have been used. Cisplatinum+vincristine+bleomycin chemotherapy plus radiation treatment was reported to have a 2-year survival rate of 67.7%, which was higher than 46.5% after radiotherapy alone.[56] The regimen of cisplatinum+etoposide/carboplatin+etoposide was effective in the intermediate group but ineffective in the poor prognosis group.[56] Matsutani et al[56] reported poor results of the regimen of ICE: ifosfamide+cisplatinum+etoposide, and that 4 of 9 patients experienced disease progression during the treatment and died within 10 months.

Because about 50% of patients treated with chemotherapy experienced recurrent disease, some researchers recommend CSI for the intermediate and poor prognosis groups after chemotherapy at a dose of 30 to 36 Gy with a boost to the primary tumor site for a total of 54 to 60 Gy.[56]

Robertson et al[57] administrated multi-modality "sandwich" therapy (chemotherapy–radiation–chemotherapy): 3 or 4 cycles of neoadjuvant chemotherapy with cisplatinum and etoposide+radiation therapy+4 cycles post-radiation chemotherapy with vinblastine, bleomycin, etoposide, carboplatin in 18 patients with non-germinomatous IGCTs, and identified that the 4-year actuarial event-free and total survival rates were 67% and 74%, respectively. Kretschmar et al[58] believe that a pre-radiation chemotherapy is effective as there is a response (complete remission, partial remission or stable disease) rate of 55% on nongerminomatous germ cell tumors. It might be possible to improve the prognosis by using a high dose of chemotherapy and radiotherapy.

Actually, the so-called neoadjuvant therapy (chemotherapy+radiotherapy and then surgical treatment followed by second chemotherapy) might be considered more strongly in the poor prognosis group,

as there is often dissemination to the CSF pathways at diagnosis or due to surgical treatment. Kochi et al[1] reported that the 5-year survival rate was 90.0% in 11 patients with non-germinomatous IGCTs receiving neoadjuvant therapy. Weiner et al[59] reviewed 126 patients with IGCTs, only 10 patients had residual tumor after pre-operative chemotherapy.

Gamma knife surgery

Recent reports have suggested that gamma knife surgery is effective for the intermediate group. Huang et al[60] carried out a retrospective review about 15 cases of immature teratoma and demonstrated a significant difference in survival curve between the gamma knife group and non-gamma knife group (P=0.0049). All of the patients with immature teratoma who underwent gamma knife surgery were alive at 5 years after surgery. Among them, 9 patients received radiotherapy and 7 received chemotherapy after initial tumor resection, showing no significant effect on the 5-year survival rate (P>0.05). This result suggests that gamma knife is highly sensitive to residual tumor, although further studies are required to confirm the conclusion. There are also a lot of clinical analyses concerning the effects of gamma knife on IGCTs, showing a control rate of 50%.[61-63]

High-dose chemotherapy (HDC)+autologous hematopoietic stem cell transplantation (AHSCT)

For the poor prognosis group, especially recurrent tumor, HDC+AHSCT was reported appropriate when tumor was completely remitted after chemotherapy.

Tada et al[64] analyzed 6 cases of non-germinomatous malignant germ cell tumors (2 cases of embryonal carcinoma, 1 case of endodermal sinus tumor, and 3 cases of choriocarcinoma). None of these cases had tumor recurred after treatment with HDC (cisplatinum 200 mg/m^2 +etoposide 1250 mg/m^2+ACNU150 mg/m^2) +AHSCT in the follow-up period (9-95 months).

Surgical management of suspected IGCTs: endoscopic or open surgery?

Since most of tumors are suspected to be IGCTs located in the pineal region and sellar region, the surgical risk of open microsurgical excision is high. An alternative to open microsurgical excision is endoscopic third ventriculostomy (ETV) with endoscopic biopsies (EBX) in cases of pineal region tumors associated with non-communicating hydrocephalus and recent evidence suggests superior safety, diagnostic efficacy and decreased morbidity and mortality compared with open microsurgical excision.[65-67] As a substantial number of IGCTs may be adequately treated without radical surgical removal, after enough quantity of tissue sampling is obtained and correct frozen pathological examination is made. Therefore, in many occasions for patients with non-communicating hydrocephalus and a pineal region tumor, simultaneous ETV with tumor biopsy is the most favorable initial diagnostic and therapeutic alternative.

Since its report in 1997,[68] simultaneous ETV and biopsy has become an important procedure in the early management of pineal region masses with concurrent hydrocephalus, thus combining therapeutic and diagnostic functions and reducing the total number of procedures for the patient.[65,69,70] The combined procedure also allows for sampling of CSF for tumor marker assays and examination for tumor dissemination. However, it should also be noted that ventricular CSF sampling is not considered as accurate as lumbar CSF sampling for biomarkers associated with IGCTs.[71]

Multiple studies[65,66,72,73] have demonstrated ETV's safety, diagnostic efficacy, and lower morbidity and mortality compared with conventional approaches. Recently, Thaher et al[74] also reported 11 cases of endoscopic surgery via a paramedian infratentorial supracerebellar keyhole approach (PISKA) for tumors of the pineal region. They believed that the endoscopically PISKA is a safe and effective minimally invasive approach that enables endoscopic treatment of different lesions in the pineal region, accompanied with comparable results to standard microsurgical technique but with less morbidity.

However, there were also limitations with endoscopic surgery. Luther et al[75] found that endoscopic biopsy may fail to yield an accurate diagnosis in cases of malignant non-germinomatous tumor. Therefore, they concluded that when primary germ cell tumor was considered, endoscopic tumor biopsy was suitable for patients with a negative biochemical analysis, but not for patients presenting with elevated tumor markers. Actually, germ cell tumors commonly display heterogeneity and mixed cell populations within the same tumor. This diversity makes it difficult for neuropathologists to appreciate the subtleties of histologic diagnosis when only small specimens are examined. The ability to obtain a large amount of tissue and perform more extensive tissue sampling by open resection is a clear advantage over endoscopic biopsy.[76]

There are at least 4 reasons for surgery. 1) More samples obtained during surgery provide more accurate and comprehensive understanding of histology of IGCTs. For mixed germ cell tumors, comprising 30%-40% of IGCTs, the small sample from stereotactic biopsy that may only represent germinoma or

teratomas could only lead to misunderstanding of the real histology which is the most important prognostic factor. Thereby, all patients should take surgical confirmation in diagnosis to assure the appropriate treatment.[77] 2) Craniotomy is more convenient to control intracranial hemorrhage than other treatment strategies. 3) Although more and more researchers are arguing that imaging suggestive of a germ cell tumor plus serum marker elevation means a malignant status, and that the patients should be treated with radiation therapy and chemotherapy without the need for biopsy, some patients with mixed germ cell tumor exhibit no elevation of serum tumor markers before surgery. Moreover, for these patients, histology sample obtained during surgery is very important.[57] 4) Surgery can prevent tumor apoplexy. Shinoda et al[78] reported that out of the 66 cases of IGCTs with a high level of HCG, 22 suffered from tumor apoplexy (5 cases of tumor apoplexy related to radiotherapy, and 4 related to stereotactic biopsy). The authors claimed that surgical treatment was suitable for IGCTs with high HCG, since tumor apoplexy was a main reason for early death.

Conclusions

According to recent cellular and molecular evidence, IGCTs, in contrast to extracranial germ cell tumors, might arise from the transformation of endogenous brain cells. The findings in the molecular characterization suggest that *CCND2*, *RB1*, and *PRDM14* play an important role in the pathogenesis of IGCTs, and the inhibition of KIT/RAS activation and the AKT1/mTOR pathway are proposed as potentially promising therapeutic strategies. IGCTs should be strictly classified according to their pathological categories before administration of pathology specific standard treatment. Although its utility remains controversial for germinoma, surgery, whether open microsurgical excision or endoscopic surgery, remains an important aspect of the diagnosis and treatment of IGCTs. It not only helps in decreasing intracranial pressure and reducing hydrocephalus but also, more importantly, gets pathological results to find the appropriate treatment. For germinoma, radiotherapy with or without chemotherapy is effective. For mature teratomas, total tumor removal is recommended. In the intermediate prognosis group, total resection combined post-operative chemotherapy, radiotherapy and/or gamma knife surgery will be the best choice. In the poor prognosis group, maximal resection combined with more intensive chemotherapy and radiotherapy is currently the best therapeutic option; however, treatment results remain unsatisfactory.

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