LETTER

No clear evidence for an association between GH replacement and relapse of intracranial germ cell tumours: single centre and KIMS experience

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GH replacement (GHR) is well established, and has been widely accepted to be safe in patients with a wide spectrum of pituitary pathologies. However, GHR in patients with treated germ cell tumours (GCTs) remains controversial, and its use has been cautioned (1, 2). Anecdotal experience from our centre and elsewhere (1–3) suggests that vigilant monitoring is mandatory in treated GCTs who are GH replaced. There are no published studies of long-term outcome and recurrence rates after GHR in treated GCTs. We have therefore surveyed our long-term experience with GHR in 18 adult patients with previously treated GCTs and a global experience of 142 patients from the KIMS database (Pfizer International Metabolic Database) in this diagnostic category in order to determine whether GHR plays a role in tumour relapse.

This is a longitudinal observational study reporting a single centre experience and global experience using the KIMS database. The study groups comprised 18 consecutive patients with GCT treated at St Bartholomew’s Hospital, London (SBH) (median duration of follow-up from diagnosis of GCT 13 years (range 0.5–44)) and 142 patients with GCT enrolled in the KIMS database (median duration of follow-up 14.8 years (0.7–36.4)). The relapse rates pre-GHR and during GHR and relapse-free survival were evaluated.

The characteristic and treatments of SBH and KIMS patients are shown in Table 1. In the SBH cohort, there were three relapses prior to GHR. All three patients had a histological diagnosis of non-germinomatous GCT (NGGCT), and had been treated with chemotherapy and/or surgery as primary treatment; radiotherapy was subsequently used after first relapse of disease; none of the patients received radiotherapy or craniospinal irradiation (CSI) as initial treatment. Four patients, two with germinomatous GCT (GGCT) and two with NGGCT, relapsed after GHR. Of the patients demonstrating a first relapse, only one had been treated previously with CSI. One patient relapsed prior to GHR, and was retreated successfully with external beam radiotherapy to the primary site of disease together with chemotherapy, but subsequently also relapsed after GHR. The estimated relapse rates were 240 and 323 per 10,000 patient-years, pre-GHR and during GHR respectively. The relative risk (RR) of relapsing after GHR was 1.34 (95% confidence interval (95% CI): 0.23–7.83; P=0.73).

Five instances of relapse were reported during KIMS follow-up. Of interest, two of these patients had never been treated with GHR (true naïve) before KIMS entry. The most relevant comparison of relapse rate during versus prior to GHR is for true naïve patients. This group had a RR of relapse during KIMS of 3.40 (95% CI: 0.26–101.4; P=0.36). For the semi- and non-naïve patients (previously treated with GH within 6 months or <6 months before KIMS entry), the RR of relapse during KIMS was statistically similar to the true naïve group, or 2.62 (95% CI: 0.45–15.3; P=0.27). RR for naïve versus semi- or non-naïve patients (including pre KIMS experience) was 1.36 (95% CI: 0.28–5.46; P=0.65), indicating similar reported relapse rates between true naïve and those not true naïve. For all KIMS patients, the estimated relapse rates were 26.6 and 77.2 per 10,000 patient-years, pre-KIMS and during KIMS entry respectively. The RR of relapse during KIMS for all patients was 2.90 (95% CI: 0.73–12.13; P=0.13).

Our results do not support the hypothesis that GHR increases the recurrence of GCT. In view of the relative rarity of intracranial GCT, we elected to utilise longitudinal follow-up and calculation of relapse frequency expressed per patient years. Despite the variation in treatment modalities, there appeared to be similar relapse rate before and after exposure to GHR in the SBH cohort. Of particular interest, most relapses were NGGCT, which is well known to have a higher risk of relapse. Furthermore, the risk of relapse is also enhanced with the lack of use of radiotherapy as primary treatment. In general patients with NGGCT and those not treated with CSI appeared to have a worse relapse-free survival but no statistical significance was observed. The data from the KIMS do not provide evidence for an association between GHR and relapse. The KIMS relapse rate appears to be lower pre-KIMS than during KIMS, but the difference was not statistically significant. The disparity in recurrence frequency between the SBH and
KIMS cohorts may be due to a number of confounding factors including selection bias for enrolment in KIMS, the variability in the frequency of surveillance imaging in contributing centres and particularly the possibility that early relapses prior to KIMS entry are under reported.

Our findings have important implications for long-term care of these patients. It has been reported that 60% of patients with GCT are hypopituitary before radiotherapy (4). The safety of GHR in intracranial GCT has been uncertain, and caution has been applied to commencement of therapy. However, our findings, derived from two independent sources, failed to find evidence to indicate a role of GHR in promoting recurrence in patients with intracranial GCT. The unpredictable nature of these tumours clearly necessitates periodic surveillance imaging but our observations indicate that this group of patients should not be denied GHR when clinically indicated. We would suggest regular periodic magnetic resonance imaging surveillance in all patients with intracranial GCT, independent of GHR.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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