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Original Research

Intermediate prognosis in metastatic germ cell tumours—outcome and prognostic factors

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Abstract ***Background:*** For metastatic germ cell tumour patients with intermediate prognosis (IPGCT) according to the IGCCCG classification 5-year overall survival (OS) rates of 79% were described, but recent data suggest significant changes.

Patients and methods: To compare the outcome of current IPGCT with former patients and to find new prognosticators a retrospective observational study was performed. Eligibility criteria were: age ≥16 years, diagnosed between 1979 and 2014. Primary end-point was the 5-year OS rate.

Results: This database includes 707 IPGCT: group 1 was diagnosed 1979–1996 (n = 237), and group 2 1997–2014 (n = 470). Median follow-up was 8.6 years (IQR: 14.4). Group 1 and 2 received first-line treatment with BEP (median 4 cycles; range 1–6) in 99% (group 1) and 95% (group 2), respectively. The proportion of first-line chemotherapy responders (CR and marker negative PR) was similar: 94% (group 1) and 96% (group 2), respectively

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($P = 0.290$), but OS was superior in group 2 with a 5-year OS rate of 89% compared with 83% in group 1 ($P = 0.035$). In refractory disease, high-dose chemotherapy and treatment beyond second line was performed more often in group 2. A lactate dehydrogenase (LDH) cut-off value of 2 ULN ($P = 0.002$; HR 2.121) and alpha-fetoprotein (AFP) levels of 6200 IU/ml ($P = 0.032$; HR 2.155) pre-chemotherapy were independent prognosticators for OS in a multivariate analysis.

Conclusion: Outcome of IPGCT has improved and is now closer to the good prognosis category. LDH and AFP levels represent potential markers to stratify IPGCT before treatment initiation.

1. Introduction

To achieve appropriate risk-based treatment decisions, a prognostic factor-based staging classification for patients with metastatic germ cell tumours (GCTs) was introduced in 1997 by the International Germ Cell Cancer Collaborative Group (IGCCCG) [1]. Defining independent adverse factors, seminoma and non-seminoma patients were categorised into three prognostic groups (good, intermediate and poor prognosis). Approximately 26% of these patients were classified as intermediate prognosis. Intermediate prognosis in metastatic germ cell tumour patients (IPGCT) is defined by the presence of either alpha-fetoprotein (AFP) values of 1.000–10.000 IU/ml, human chorionic gonadotropin (HCG) levels of 5.000–50.000 IU/l, lactate dehydrogenase (LDH) levels between 1.5 and 10 times the upper limit of normal range for non-seminomatous gonadal and retroperitoneal primary tumours, or the presence of non-pulmonary visceral metastases for those with pure seminoma. The 5-year overall survival (OS) rate for IPGCT was 79%, but data for IGCCCG were retrieved in the 1970–80s, and outcome has presumably improved over time [2–5]. Current guidelines still recommend four cycles of platinum-based chemotherapy for the intermediate- and poor prognosis category, possibly leading to over-treatment for IPGCT [6–9]. To investigate the current outcome of IPGCT and to find novel prognosticators, we established a large database.

We hypothesised that the IGCCCG classification underestimates the current outcome and that some IPGCT may be over-treated. We aimed to address these critical issues and provide original insights into the current prognosis of IPGCT and to define novel prognosticators.

2. Patients and methods

2.1. Study population

Data were collected retrospectively from 15 centres across Europe, the Russian Federation, Australia, and the USA and entered into a central database located at University Medical Center Hamburg-Eppendorf, Germany. The study protocol and data processing were approved by the local ethics committee. Participating centres were members of the global germ cell tumour collaborative group G3 or the German germ cell cancer collaborative group.

2.1.1. Inclusion criteria

Patients had to fulfil the following inclusion criteria: intermediate prognosis according to IGCCCG criteria, male sex, age $\geq$16 years; GCT defined either histologically and/or by serum tumour markers in the intermediate range (HCG or AFP or LDH) obtained before chemotherapy, diagnosed between 1979 and 2014; and availability of baseline and follow-up information including first-line treatment modalities to calculate primary and secondary outcome variables.

2.2. Statistical analysis

Objectives of this project were to test whether the outcome of IPGCT improved since the implementation of the IGCCCG classification and to find new prognosticators. Primary end-point was the 5-year OS rate; secondary end-points were progression-free survival (PFS) and treatment response. OS was calculated from the date of primary diagnosis until death from any cause. PFS was defined from the start of first-line chemotherapy until progression of disease or last day of follow-up. Patients dying without progression were censored at the time of death. Patients lost to follow-up were censored at the date of last visit. Covariates evaluated as potential prognostic factors were histology of the primary tumour, presence/absence of metastases to the following organs e.g. lymph node involvement, lung, number of metastatic spread (1 versus 2), localisation of the primary tumour (gonadal versus extragonadal), tumour markers prior chemotherapy (including AFP, HCG and LDH), and the course of tumour markers ($t_{1/2}$ for AFP of $\leq$7 days and/or for HCG of $\leq$3 days) during first treatment cycle if available [10]. Calculation of correlations between different