Dose dense chemotherapy for untreated poor prognosis and relapsed germ cell tumours – An 18 year experience with GAMEC chemotherapy.

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Abstract

Background

The role of dose intensified cisplatin-based regimens as alternatives to conventional Bleomycin, etoposide and cisplatin (BEP) based treatments in untreated poor risk testicular cancer, and their utility in recurrence following first line chemotherapy remains unresolved. Here we report a single Centre experience of the regimen GAMEC (granulocyte colony stimulating factor, actinomycin-D, methotrexate with folinic acid rescue, etoposide and cisplatin) over 18 years in both untreated and relapse settings.

Methods:

This retrospective cohort study is based on 162 patients who received the GAMEC– both dose dense chemotherapy and incorporation of actinomycin and methotrexate. Survival outcomes were compared and risk categorisation methods of the IPFSG and also based on LDH>ULN and Age>=35 were compared in terms of survival outcomes using Cox proportional hazard regression modelling.

Results

Seventy five patients with IGCCCG poor prognosis disease received GAMEC as initial therapy. With a median follow-up of 63 months, median PFS was >14 months. Two-year progression free survival (PFS) rate was 61.5% (95% CI: 49.1-71.6) and the 3-yr overall survival (OS) was 71.9%. Seventy six received GAMEC as second line (following failure of BEP or EP). The median PFS was 7.5 months (95% CI: 5.2-NE), the 2-yr PFS rate was 43.5% (95% CI: 32.1-54.4) and the 3-yr OS was 53.7% (41.6-64.3). In the 3rd line setting (n=11) the 2y PFS was 18.2% (95%CI: 2.8-44.2). Overall, the TRD rate declined from 10.5 % in the first 15 years to 2.6% in the last 5 years.

Conclusion

GAMEC is an effective regimen in untreated poor prognosis disease and on relapse following conventional cisplatin and etoposide based chemotherapy. Risk categorization based on LDH/Age is more sensitive than IPFSG2 criteria. It is possible to identify patients particularly likely to benefit from this treatment whose short duration and absence of bleomycin are significant advantages, particularly in patients with central nervous system and mediastinal disease. Low dose induction treatment is associated with safer delivery of treatment without compromising survival.

Introduction

Metastatic germ cell tumours are curable with modern therapeutic approaches utilizing cisplatin based chemotherapy and surgery to resect residual masses.

Much progress has been made through randomized studies that have resulted in Bleomycin, Etoposide and Cisplatin (BEP) delivered in three weekly cycles becoming standard care for most patients who present with metastatic disease. However in terms of improving cure rates two main areas remain challenging, that of poor risk treatment naïve disease and relapse following first line chemotherapy. Those de novo cases who present with very advanced disease (deemed "poor prognosis" by the IGCCCG 1997 classification (1)–include patients with very high serum tumour markers and/or those with adverse metastatic sites – liver, bone, brain (or other non-pulmonary visceral sites). These patients can expect a cure rate of only 40-50% with standard BEP chemotherapy. Previous randomized studies intensifying cisplatin dose alone have shown no benefit in failure free survival in poor risk disease, and indeed escalating to high dose triplet chemotherapy with stem cell support (2) showed no improvement in failure free survival in the high dose arm.

However single centre and multicentre randomized phase II data (3) (4) (5) (6) has suggested that more intensive up front protocols with exposure to a regimen containing a greater variety of cytotoxic agents than in BEP yielded improved results in terms of progression free survival in the untreated setting in poor risk disease compared to conventional BEP but at the cost of increased toxicity. Two recent multi-centre randomised studies of dose intensified multiagent regimens appear to confirm this experience with improved progression free survival compared to 4 cycles of BEP (7) (8) , both are bleomycin containing.

Similarly the 20-30% of patients who relapse following initial cisplatin based combination chemotherapy can expect a cure rate of 40-60% with conventional dose Ifosfamide based regimens (9, 10)

In patients who relapse following initial therapy various factors influence potential chemo-sensitivity, including histology at diagnosis, time to recurrence, sites of recurrence and height of tumour markers at relapse. These have been developed into the International Prognostic Factor Study Group (IPFSG) scoring system. They do not include age (11) nor LDH despite this being included in the de- novo IGCCCG prognostic groups (1) . We had previously noted that both these were prognostically significant (12) .

The optimal therapy in this group remains unclear with cisplatin and ifosfamide based 3 weekly treatments being the most popular without any randomised comparison supporting the choice of one over another. High dose chemotherapy and autologous stem transplantation is often used to consolidate 2nd or subsequent relapse (13). Retrospective data suggest high dose treatment produces more favourable outcomes at first relapse in the IPFSG intermediate and poor risk categories (14).

In this context, we developed the GAMEC regimen (granulocyte colony stimulating factor, actinomycin-D, with high dose methotrexate and folinic acid rescue, etoposide and dose dense cisplatin) in 1997 (5) . This article reports on a high volume single referral centre experience of the dose intense regimen GAMEC in a large and mature cohort. Progression free survival (PFS), overall survival (OS) and treatment related death (TRD) are explored in light of emerging data on the utility of dose intense approaches in this disease.

Methods:

This is a retrospective cohort study based on St Bartholomew's Hospital treated using the GAMEC regimen. GAMEC (see **Figure 1**) incorporated two strategies – dose dense chemotherapy as had been described by Wetlauffer and incorporation of actinomycin and methotrexate(15) - both used in upfront treatments (3) and described in the salvage setting (16). The dose of methotrexate was high with the intention of enabling treatment of brain metastases without additional radiotherapy. Cisplatin 100mg/m2, actinomycin 1mg/m2, methotrexate 8g/m2 adjusted for renal function and etoposide 360mg /m2 were administered every 2 weeks with cisplatin 50mg/m2 one week later for the first two cycles. Initially 5 cycles were planned. It became clear that the 4th and 5th cycles were often delayed and required dose reduction – so they were dropped in stages. Initially this was for relapsed patients who were younger (< 35) and who had a normal LDH but subsequently for other patients as well. We substituted epirubicin for etoposide as part of a prospective study in patients who were older and with a high LDH- the results were identical and the study

was closed [Benafif S.2015. "Is short duration chemotherapy possible for relapsed germ cell tumours?" In *British Uro-oncology Group annual meeting*, e7. York, UK]. From the beginning ill patients with compromised renal function, poor performance status or heavy tumour burden were offered induction treatment with cisplatin 50mg/m2 , vincristine 2mg and bleomycin 30000 units (baby BOP) with the aim to start GAMEC within 11 days (17) . Consecutive patients who received GAMEC chemotherapy (**Table 1**)– both as part of studies and subsequent patients treated following study closure were reviewed. Attention was paid as to whether patients had received low dose induction chemotherapy with baby BOP. Patients who received GAMEC who were left with residual masses had these surgically removed where possible. Those that contained viable cancer did not go on to receive further treatment in the absence of progression. The outcome and success of further treatment is described. Dose reductions were made according to the following approach. Patients who were over 30 had their methotrexate dose capped at 8g/m2. Patients who had evidence of ureteric obstruction on CT were given 50% of the methotrexate dose planned from the EDTA clearance. On the first cycle day 8 was omitted if the patient received induction therapy with baby BOP (cisplatin 50mg/m2, vincristine 2mg and bleomycin 30,000 units over 12 hours). To go ahead with each cycle required a neutrophil > 1x106/l and platelets of > 60x106/l (and rising). Urea and electrolytes were measured daily during chemotherapy and every 48 hours until recovery of the full blood count. Patients who were out of hospital who experienced a greater than 20% rise in serum creatinine were admitted for hydration. Patients who had neutropenia < 0.5x106/l for 5 or more days or whose platelet nadir was < 20x109/l received a 20% dose reduction in all drugs except methotrexate. Methotrexate doses were specifically reduced if there were grade 3 or above mucositis. If the creatinine rose by > 20% a repeat EDTA was carried out and doses of methotrexate based on this. Further reductions following the second cycle were made using the same approach.

Treatment of patients

Out of the 162 patients included in this study, 62 were treated as part of the initial GAMEC study, and thirty six were treated as part of the GAMEC 2 study

where patients with high LDH or were over 35 received epirubicin 60mg/m2 instead of etoposide 360mg/m2 and where as those who did not have these risk factors received 3 cycles only of GAMEC over 6 weeks. The other 64 patients were treated outside the study and received the therapy as standard of care on relapse or were offered it as an alternative to conventional BEP in the untreated setting if they had IGCCCG poor prognosis disease (**Table 1**).

Statistical methods

Progression free survival (PFS), Time to progression (TTP) and Overall survival (OS) were measured from the date of study enrolment to the date of disease progression or death. Patients who didn't die or progress were censored at the last date of follow-up. Patients who died were considered as event for PFS, while they were considered as censored in the calculation of TTP. PFS, TTP and OS were compared using Kaplan Meier curves with log-rank tests. Our classification based on Age and LDH was also compared with the classification of patients using IPFSG using Fisher's exact test. Survival outcomes according to IPFSG and Age/LDH risk categorization among 2nd line GAMEC patients were compared using chi-squared test for trend. Risk categorisation methods of IPFSG and Age/LDH were also compared using univariable as well as multivariable Cox PH regression model among 2nd line GAMEC patients.

Results

162 patients received GAMEC between September 1997 and November 2016. Seventy five patients received GAMEC (**Figure 1**) as initial treatment while 76 received as second line, 9 as third line and 2 as fourth line treatment. (**Table 1** describes patient characteristics) Kaplan-Meier curves for progression free survival (PFS) and overall survival (OS) are presented in **Figure 2**.

Out of 75 patients receiving GAMEC as first line in poor risk disease, 34 had a histological diagnosis and 41 were diagnosed on the basis of markers alone. Forty five were gonadal, 24 mediastinal, 6 other extra gonadal. In 42 this was preceded by baby BOP induction treatment (**table 1**).

With a median follow-up of 63 months, the two-years PFS rate was 61.5% (95% CI: 49.1-71.6), see **Table 2**. Forty-eight were progression-free to GAMEC. Two of

these died of other causes in remission –one of acute myeloid leukaemia – a known associated malignancy with mediastinal non-seminomatous germ cell tumours and one of lymphohaemophogocytosis.

Forty-one had post-treatment resections of whom the pathology is shown (**Supplemental Figure 3a**), 35 were had a surgically confirmed complete remission (no evidence of disease, With either necrosis or teratoma). Three subsequently relapsed. Six had viable cancer at operation of whom 4 relapsed. Thirty four did not have surgery. There were 17 relapses and 5 treatment related deaths with neutropenia; of the 24 relapses, 7 were cured by further therapy (including high dose chemotherapy)

Relationship between low dose induction treatment and treatment related deaths

Forty two (56%) patients received baby BOP (bBOP) induction treatment – there were no treatment related deaths in this group. Two-years PFS rate (58.6% vs 65.2%, P=0.67) and TTP rate (63.1% vs 76.9%, P=0.19) were less to bBOP – which were not significant and overall survival was not compromised either (70% vs 74.2%, *P*=0.98) (**Table 3**).

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Mediastinal non-seminomatous germ cell tumours

There was no evidence that patients with mediastinal primaries (n=24) fared any worse than those with non-mediastinal primaries. (55.4 vs 64.2% progression free at 2 years with 62.4 vs 75.7% alive at 3 years (P=.13). In those with no distant metastases were who were poor prognosis by markers alone (n=12) (i.e. no adverse sites of metastases the PFS and OS were 79% at 2yrs and 87% at 3yrs respectively). In those with metastases the corresponding results were 36% and 34% respectively.

Brain metastases

Ten patients presented with brain metastases, 13 patients with brain metastases received GAMEC as first line salvage. No routine cranial irradiaton was administered. There was no statistically significant difference between those

who presented with brain metastases and those other IGCCCG poor prognosis patients 50% PFS at 2 y vs 63.3%) or overall survival at 3 y (66.7% vs 72.6%). In the relapse setting the results of patients with brain metastases showed a PFS of 50% vs 46.5% in the rest and an overall survival of 47.6% vs 54.9% .

Further treatment

Twenty one patients went on to have further treatment. In 18 (86%) stem cell collection for high dose chemotherapy was attempted. In one patient insufficient stem cells could be mobilized. All these patients received oxaliplatin, irinotecan and paclitaxel (IPO) and then high dose carboplatin, thiotepa and topotecan. 6 (29%) were cured by this. In two patients there was progression on IPO – these had a further attempt at chemotherapy prior to receiving high dose chemotherapy – which failed in both cases. The patient who could not be successfully mobilized was cured by IPO alone. Overall 75% were cured.

GAMEC for recurrent disease.

A total of 87 patients received GAMEC as subsequent therapy. Seventy six received it as second line, 9 as 3rd line and 2 as 4th line. For those who received it in the second line setting 91% received cisplatin and etoposide based therapy. 3% received carboplatin based combination chemotherapy as their first line therapy.Seventy-six patients received GAMEC in the second line setting. Their average age was older (33 y vs 30 y for those untreated). Proportionately fewer patients received low dose induction treatment as most of these patients had lower tumour burdens at the time of recurrence, borne out by lower tumour markers. There were 7 TRDs (9.2%). the the median PFS was 7.5 months. Two-years PFS rate was 43.5% (95% CI: 32.1-54.4), see Table 2. Thirty-seven (49%) of patients had surgery for residual masses (**Supplemental figure 3B**). Necrosis/ teratoma was seen in 22 of whom 5 relapsed and viable cancer in 15, of whom 10 relapsed. Thirty nine did not have surgery – 24 relapsed, 8 were progression free. We identified 2 prognostic factors from our original series, namely raised LDH at relapse or being aged 35 or older Fourteen patients (18%) were treated as part of a risk adapted strategy where epirubicin 60mg/m2 was substituted for etoposide in patients with at least one of these risk factors and the remainder

received only 3 cycles of GAMEC. The overall outcome was as follows. Forty three percent of patients were progression free at two years to GAMEC and appropriate surgery of those who received epirubicin substituted GAMEC- (high LDH and/or 35 or older) 2 were PF. Those lacking these risk factors were given 3 cycles of GAMEC of them 9 were progression free.

During the period covered the international prognostic factors study group (IPFSG) published their prognostic factors-they did not include age or LDH but instead used – sites of relapse, tumour markers and response to initial therapy (11).This gives an opportunity to classify relapse using this scheme – the outcomes are shown in **Table 4 and Supplementary Table 5**. There is a clear decreasing trend of PFS, TTP and OS with the increase of the number of bad factors (LDH or age). However, this is not the case in case of IPFG2 classification.

Using LDH and age to separate patients 35 (45%) had neither prognostic factor – their 2 year PFS was 67% with a 3 year overall survival of 73%. Thirty patients (39%) had one adverse factor – their 2 year PFS was 29% with a 3 yr overall survival of 38%. Eleven (14%) had both adverse factors their 2 yr PFS was 9% with a 3 yr overall survival of 36% (**Table 4**)

Fisher's exact test between the categorization of 2nd line patients based on IPFSG2 and Age/LDH (0, 1, or 2 bad factors) show that they are not associated (*P*=0.43)

Supplementary Table 5 shows univariable analysis using Cox regression shows that both factors LDH>ULN and Age>=35 have significant effect on the three survival outcome measures. However, only high IPFSG2 category had significant effect on survival outcomes. While both IPFSG2 and LDH/Age categorization methods included in the model in multivariable setting, IPFSG2 categorisation was not a significant predictor of outcome.

Further treatment

Thirty-three (43%) cases went on to receive third line therapy after GAMEC. In 70% of cases it was with high dose chemotherapy and a stem cell transplant. In 22 cases this was with oxaliplatin, irinotecan and paclitaxel (IPO) induction

followed by HDCT (18) of whom 5 were progression-free. In 1 it was with Paclitaxel, ifosfamide and cisplatin (TIP) and HDCT – this patient was progression-free. One additional patient who failed IPO and HDCT was subsequently cured using gemcitabine and docetaxel. Overall 7 patients (27%) were cured in this setting leading to an overall cure rate of 51%.

Third line therapy

Nine patients received GAMEC in the third line setting – 2 were rendered PF by this. There were 2 treatment related deaths. Both patients had received BEP as first line therapy. Neither had received high dose chemotherapy. Two patients received GAMEC in the 4th line setting; both died of disease.

Treatment related deaths in GAMEC

There were 14 (8.6%) treatment related deaths in patients receiving GAMEC There were 5 treatment related deaths in the first line setting (6.7%) and 9 in the salvage setting (9.2%) .The most frequent cause was neutropenic sepsis. Colitis was seen including one case secondary to invasive aspergillosis. Patients receiving the treatment as first line therapy had a lower rate (6.5%) than those who received it as salvage therapy – (10.6%) with the highest proportion of deaths who received it in the third line setting. This is not entirely surprising – the treatment is very myelosuppressive and bone marrow reserve When looked at over time, it is clear that refining of dose reductions has played a role in making the therapy safer. In particular dose reductions following prolonged cytopenias on previous cycles. This is borne out by the fact that in the last 4 years (38 patients) there has been 1 death (2.6%). Overall, the TRD rate declined from 10.5 % in the first 15 years to 2.6% in the last 5 years.

Secondary malignancies

There were 6 recorded second malignancies. Two were contralateral stage 1 seminomas. In one patient – aged 44 this was 11 years following 3rd line GAMEC. In the other aged 31 it was 3 y post second line GAMEC. I patient developed myelodysplasia 18 months post 1st line GAMEC for a testicular poor prognosis metastatic GCT .He was24 and had received 3 cycles only. In the other patient with a mediastinal GCT he was found to have acute myeloid leukaemia a few

months post completion of therapy when he had persistently low platelet counts. He died of this. One patient had an incidental RCC picked on routine imaging 11 years post GAMEC for relapsed disease he was 49 and successfully treated by surgery. One patient developed small cell lung cancer 7 y post GAMEC at the age of 60 he had been a heavy smoker and died of this condition. One patient developed a cancer of the anterolateral margin of the tongue 3 years post second line GAMEC treated successfully by surgery. He was 37.

We looked at how many cycles were received and the outcome in **Supplementary Table 6**. In untreated patients, there was a significant declining trend in PFS and OS among patients in terms of 5 cycles, 4 cycles and 3 cycles (where a deliberate decision to stop at 3 was made) of treatment.

In previously treated patients who received only 4 cycles fared significantly worse that those who received 3/5 cycles. However this is confounded by the fact that in GAMEC-2 study, those with no bad factors (LDH/age) were allocated 3 cycles and the other received 5 cycles with epirubicin substitution.

Discussion

This report details a single centre experience using a chemotherapy regimen in germ cell tumours utilizing high dose methotrexate both in the untreated poor prognosis group and also on relapse following failure of conventional cisplatin based chemotherapy. It is unusual for a single regimen to be used in both settings. The single centre nature is clearly a weakness of this report but long term follow up data is mature in this cohort and the number of patients treated offers insights into the nuances of delivering dose intense therapies. A weakness of the data is that given that the data is collected over 18 years there are likely to have been changes and modifications in supportive care not quantified over this period that have impacted outcomes. This may particularly explain an improvement in treatment related morbidity over the last 5 years.

There has been a long running debate about whether more intensive regimens are able to better the results of BEP in poor prognosis disease. Recently two

randomised studies have confirmed better progression-free survival. Indeed this was suggested much earlier in 1997 when a review of the POMB-ACE data was presented (3)

It would seem that the balance of evidence supports the hypothesis that patients with poor prognosis disease who tolerate a more intensive treatment are less likely to require salvage therapy. The results with GAMEC in the first line setting are comparable with those see with other previously reported dose intense approaches (19) (20) (7, 8, 21). This is potentially an advantage in both older patients who are likely to tolerate further therapy less well, as well as younger patients where requirement of more chemotherapy is associated with a greater risk of cardiovascular, neurological disease as well as second malignancies.

GAMEC is bleomycin free –hence lending it self to use in the second line setting following BEP and also being advantage in the first line setting when patients have extensive pulmonary disease and thus a greater risk of lung damage. It has become clear that patients with mediastinal non seminomatous germ cell tumours are a particular group where bleomycin related toxicity seems a problem (22) hence the suggestion to use ifosfamide instead (23).

This does not seem to be a problem encountered with GAMEC. There does not appear to have been an excess of post surgical complications and patients with no metastases outside the mediastinum are now being given only 3 cycles prior to surgery. Patients with brain metastases at presentation seem to have a good outome. No untreated patients received radiotherapy and in the relapse setting radiotherapy was only used where surgical verification of residual masses did not prove possible- these findings have been described previously (24, 25). Pathological findings of viable cancer post chemotherapy was associated with poorer outcomes as seen in other series (26).

In patients with brain metastases at presentation the PFS expected with BEP has been shown to be approximately 30% (27) with a 3 year OS of 50%. The data presented here and previously (25) has shown impressive progression free and

overall survival in this group of patients compared to that expected with conventional BEP chemotherapy. The use of GAMEC in these patients at first line treatment has a progression free survival at 2 years of 55% with a 3 year OS of 66%. For patients developing brain mets at relapse the PFS and OS expected with standard approaches is 21% and 27% (27). The PFS for GAMEC as second line therapy is 50% with an overall survival of 47.5%. Data presented from IGCCCG overview and GETUG-13 Study (28) has described the historically poor salvage rates for CNS progression events. This being the case we would argue that utilization of GAMEC upfront in these patients should be specifically considered.

In the second line setting – the outcomes compare favourably to other regimens when set against the IPFSG criteria. Indeed in patients who have been deemed to have intermediate or high risk disease do seem to do better than predicted. In our original series age and LDH seemed to be predictive of long-term outcome, and this has been replicated in other series of metastatic germ cell tumours(29). In this expanded series this seems to continue to be the case. Patients who do not possess either of these factors seem to do well even if they fall into relatively adverse groups using the IPFSG criteria. Importantly a significant proportion of mediastinal NSGCTs were successfully salvaged using this approach. It is worth noting that all patients who received this treatment in the second line setting had previously received BEP in currently recommended doses.

We thought it was legitimate to include patients in this series who had received epirubicin rather than etoposide as part of a study in patients who had either a raised LDH or were over 35 – because the results were superimposable for a similar cohort who had received conventional GAMEC using etoposide.

The argument about whether high dose chemotherapy should replace conventional therapy on first recurrence is contentious. Retrospective review suggests that these patients do better (14), but prospective randomised studies in this area to date have not shown a clear overall survival benefit of high dose therapy (30) (31, 32). Certainly if it is to be deferred we need to be confident that stem collections can safely be done. In this series over 70% of cases that progressed after GAMEC proceeded to receive high dose chemotherapy and a stem cell transplant – both following GAMEC as first line

therapy and when used as salvage treatment.

The treatment related deaths remain a concern, however it is clear that the treatment is becoming safer to deliver. The patients who seemed at particular risk were those received more extensive treatment, and those who received an intensive regimen prior to GAMEC. Paradoxically, those untreated patients who were ill and started therapy using baby BOP first seemed to fare better – in those patients accounting for 28% (46 patients) of the total there were no treatment related deaths compared to 13% of the rest. As the outcome was not worsened by low dose induction treatment – there is a strong argument for making this approach standard in patients who present with poor risk disease and are unwell at first presentation.

The overall reduction in treatment related deaths that has occurred with time is probably due to stricter dose reductions – particularly as far as high dose methotrexate is concerned – the drug doses seem less well tolerated in older patients independent of renal function as assessed by EDTA, which suggested other factors are important. However a weakness of the data is that given that the data is collected over 18 years there are likely to have been changes and modifications in supportive care not quantified over this period that have impacted outcomes, and this may also contribute to an improvement in treatment related morbidity over the last 5 years. This study gave different cycles of treatment depending on the age and LDH and hence it is difficult to measure the effect of number of cycles. However, there was a significant declining trend in PFS and OS among untreated first line patients with the decreasing number of cycles.

Conclusions

GAMEC would seem to have particular advantages in several patient groups in upfront treatment of poor risk disease- ie those with brain metastases at presentation and those where bleomycin poses greater risk such as primary mediastinal tumours. The progression free survival seen is superior to that which would be expected with standard of care BEP

chemotherapy, but a the cost of greater toxicity. These results have been achieved using established older cytotoxic agents. The short duration of treatment is a potential advantage when compared to other approaches, and shows that progressive refinement of a regimen can improve its safety without compromising outcome. In the pretreated patient group – those who have failed BEP or an equivalent regimen - particularly where the IPFSG grouping is intermediate or high when patients are younger (less than 35) the use of GAMEC would appear particularly suitable. The ability to collect stem cells post GAMEC and the high cumulative survival offers potential advantages over resorting to tandem or triple high dose chemotherapy on first relapse.

Information section

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All authors were involved in manuscript preparation and review.

Ethical Approval: All patients recruited to the GAMEC phase II clinical trial
signed appropriate informed consent with institutional ethical approval in place.
All patients treated subsequently were treated through the specialist MDT
according to network guidelines offering GAMEC in poor risk disease.

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Table 1: Patient and disease characteristics

Characteristics	1st line (N=75)	2nd line (N=76)	3rd line + (N=11)
Median Age, range, Years	30.1 (16-47)	33.0 (18-56)	31.3 (21-53)
Diagnosed on:			
Histology	34	50	11
Markers	41	26	0
Histology			
NSGCT	75	68	9
Seminoma	0	8	2
Primary			
Testis	45	64	5
Extra-Gonad	6	12	0
Mediastinum	24	0	6
Brain metastases	10	13	1
Markers: Median (range)			
AFP	275 (<1-58830)	4.5 (<1-760750)	26 (3-2583)
HCG	2943 (<1-2800000)	67.5 (<1-106000)	<1 (<1-562)
LDH	1030 (246-10920)	399 (2015-3434)	790 (347-1694)
IPFG2			
High – Very high	-	15	-
Intermediate	-	46	-
Very low- low	-	15	-
Induction			
Baby BOP	42 (56%)	3 (4%)	0 (0%)
Median no of cycles	4	3	2
Further Chemo	21	33	4
IPO+HDCT	15	22	1

TIP+HDCT	0	1	0
HDCT	71%	70%	25%
Surgery	41 (55%)	37 (49%)	

Table 2: Survival outcomes to GAMEC according to line of treatment.

	1st line	95% CI	2nd line	95% CI	3rd line +	95% CI
Median F/U, month	63		80		103.5	
Median PFS, months	NYR	(14-NE)	7.5	(5.2-NE)	2.1	(0.6-9.3)
2-years PFS rate (%)	61.5	(49.1–71.6)	43.5	(32.1-54.4)	18.2	(2.8-44.2)
2-years TTP rate (%)	68.5	(55.8-79.7)	48.8	(36.6-60.2)	22.2	(3.4-51.3)
3-years OS rate (%)	71.9	(58.9-81.4)	53.7	(41.6-64.3)	24.2	(4.4-52.5)

Table 3. Survival outcome to GAMEC in 1st line patients according to use of induction chemotherapy (baby BOP).

	Baby BOP induction given for 1st line				P-vale (log rank test)
	Yes	95% CI	No	95% CI	
2-years PFS rate (%)	58.6	(42.0-71.9)	65.2	(45.9-79.1)	.67
2-years TTP rate (%)	63.1	(46.3-75.9)	76.9	(55.4-89.0)	.19
3-years OS rate (%)	70.0	(51.1-82.8)	74.2	54.8-86.3)	.98

Table 4. GAMEC Outcomes in 2nd line treatment. survival outcomes according to IPFSG prognostic criteria and and Age/LDH risk categorization.

	IPFSG2			
	N	*PFS (2yrs)*	*TTP (2yrs)*	*OS (3 yrs)*
Very low-low	15	37.5%	40.4%	43.6%
Intermediate	46	55.5%	60.9%	63.8%
High-very high	15	13.3%	16.7%	33.3%
P (log rank for trend)		.09	.15	.24
	Adverse factors: Age>=35 or LDH>ULN			
Adverse factors	*N*	*PFS (2yrs)*	*TTP (2yrs)*	*OS (3 yrs)*
0	35	67.2%	73.8%	72.9%
1	30	29.1%	32.3%	38.2%
2	11	9.1%	11.4%	36.4%
P (log rank for trend)		<.0001	<.0001	.001

GAMEC - Schema

Cycle 1 (15 days)															
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Actinomycin 1 mg/m^2															
Methotrexate 8g/m^2 (dose adjusted for renal function)															
Etoposide 90 mg/m^2															
Cisplatin 50 mg/m^2															
Filgrastim 300 mcg/day															

Figure 2A: Progression free Survival in metastatic NSGCT patients treated with GAMEC.

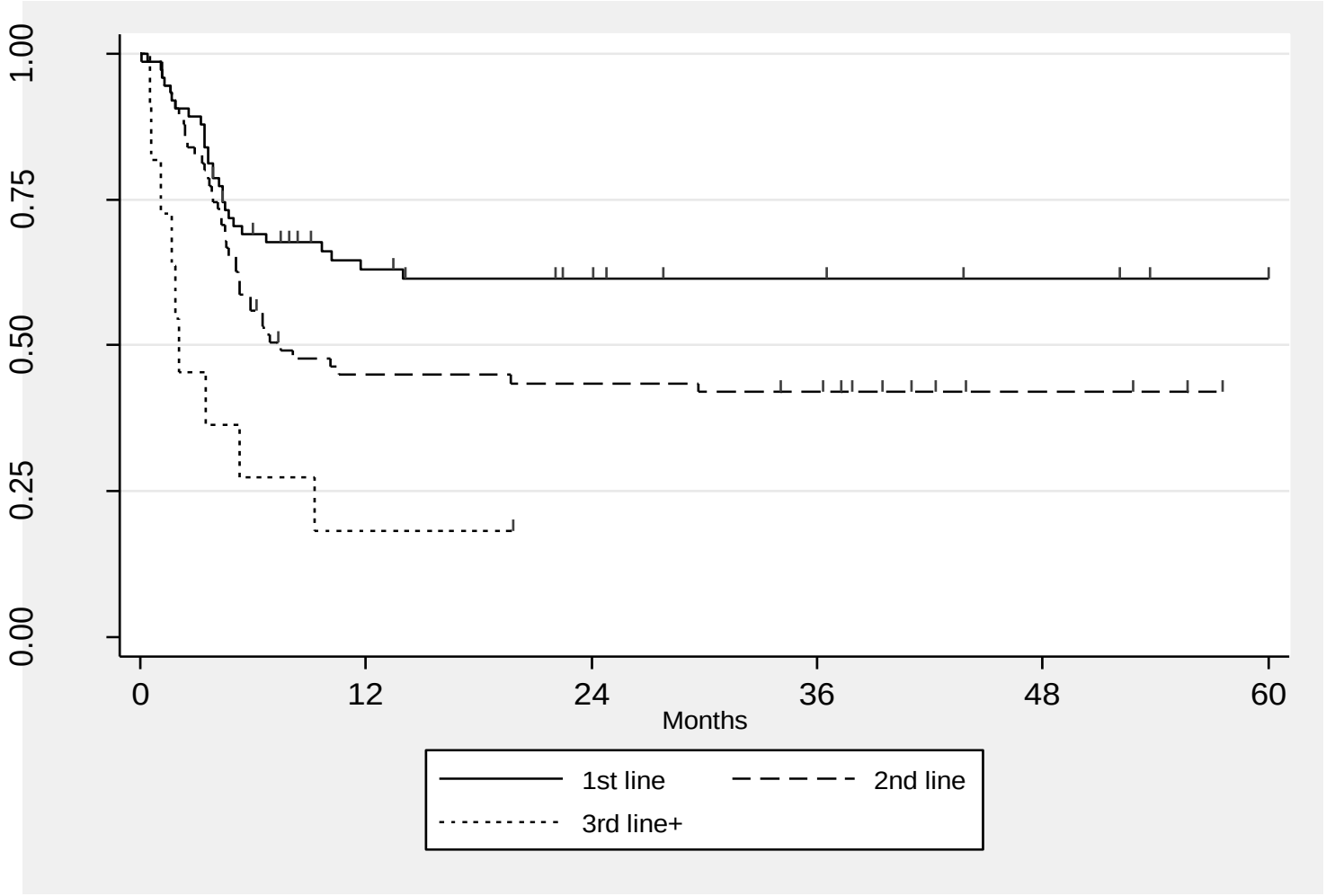

Figure 2B: Overall Survival in metastatic NSGCT patients treated with GAMEC.