CS-37

Shortlisted for Poster Award Presentation

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Unmanipulated Haploidentical Transplant with Posttransplant Cyclophosphamide vs Matched Sibling, Matched Unrelated Donor and Unrelated Cord Blood Transplant for Haematological Malignancies

Background

Outcomes after unmanipulated haploidentical (Haplo) haematopoietic cell transplantation (HCT) and after unrelated cord blood transplantation (UCBT) are encouraging and have become alternative options to treat patients with high-risk haematological malignancies without human leukocyte antigen (HLA) matched donor.

Methods

We studied 459 adults patients receiving allogeneic HCT for various haematologic malignancies between Jan 2005 and Dec 2016. The patients received HCT using 7-8/8 HLA-matched related donor (MRD, n=223), HLA-matched unrelated donor (MUD, n=118), Haplo (n=28) or 4-6/6 HLA matched UCB (n=90) graft, after myeloablative (MAC, n=288) or reduced intensity conditioning (RIC, N=171) regimen. Haplo recipients received calcineurin inhibitor (CNI), mycophenolate, and posttransplant cyclophosphamide for graft-versus-host disease (GVHD) prophylaxis.

Results

5 year overall survival for patients undergoing MRD, MUD, UCB and Haplo HCT were 45%, 52%, 41% and 44% and of disease free survival (DFS) were 42%, 50%, 35 % and 34 %, respectively; these were not significantly different among the 4 donor groups. The 24-month cumulative incidences (C.I.) of nonrelapse mortality (NRM) were 18%, 22%, 37% and 33% (p=0.007) and of relapse were 40%, 28%, 37% and 31%, respectively (P=0.226). C.I. of grades 3 to 4 acute GVHD at 6 months were 10%, 6%, 9% and 8 %, respectively (P =0.653); chronic GVHD occurred in 45%, 17%, 8% and 24% of patients, respectively (P<0.001). Despite its association with higher NRM (HR 2.54, 95% CI 1.19-5.34; p=0.015) the use of Haplo donor did not result in any statistically significant difference in DFS (p=0.108) as compared with other donors.

Conclusions

Haploidentical transplantation using unmanipulated graft and post- transplantation cyclophosphamide results in equivalent outcome to those contemporaneous HCT performed using MRDs, MUDs and UCB. It provides additional alternative for patients lacking HLA matched donors.

CS-39

Shortlisted for Poster Award Presentation

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A Descriptive Study of Viral RNA Sequences Identified from Single-Cell Analysis of Acute Myeloid Leukemia

Background

Single-cell RNA sequencing (scRNA-seq) provides single-cell resolution on the expression of genes that are normally eclipsed in bulk RNA-seq. While conventionally used to identify rare cell types and lineage, it can also detect viral RNA transcripts that may potentially be relevant to tumorigenesis. We performed scRNA-seq on 3 acute myeloid leukemia (AML) patients and ran the data through a computational pipeline for virus discovery. We found a number of cells harboring retroviral sequences such as the Moloney murine leukemia virus (M-MuLV) and murine osteosarcoma virus (MSV).

Methods

White blood cells (WBCs) were isolated from the bone marrows and were pre-stained with anti-CD34 antibody and sorted into CD34 and non-CD34 cells by cell imaging. Single-cell isolation, cell lysis, reverse transcription of mRNAs to cDNAs, pre-amplification, and harvesting of amplified products were performed by the Fluidigm C1 System. Nextera XT DNA kit was used for library preparation and paired-end sequencing was performed on the NextSeq and HiSeq. Viral identification was performed using a custom virus identification pipeline.

Results

We sequenced 212 WBCs, comprising 132 CD34 and 80 non-CD34 cells. Of the cells, 16 harbored M-MuLV sequences (CD34 (n=8); non-CD34 (n=8)), 26 harbored MSV sequences (CD34 (n=20); non-CD34 (n=6)), and 14 cells harbored ADV sequences (CD34 (n=7); non-CD34 (n=7)). Other viral sequences feline sarcoma virus, friend murine leukemia virus and Fujinami sarcoma virus were also found.

Conclusion

Although a variety of viral sequences were found, it was observed that the CD34 cell, a multipotent progenitor cell in the blood, frequently harbor MSV as compared to the non-CD34 cells. The presence of viruses in the CD34 cells may cause genetic instability and lead to alteration of oncogenes or tumor-suppressor genes. Further work is required to validate this observation and determine the tumorigenic properties of the identified viral sequences in AML.

CS-40

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Outcome and Prognostic Factors of Patients with Hematological Malignancies Admitted to an Intensive Care Unit

Background

Patients with hematological malignancies (HM) often develop complications due to their treatment or their underlying disease, requiring admission to an intensive care unit (ICU). This study aimed to study the outcomes and prognostic factors for patients with HM admitted to the ICU of a tertiary hospital.

Methods

We reviewed the case records of consecutive ICU admissions for patients under the hematology service in our institution, from July 2010 to June 2014. Clinical information was evaluated for association with the primary outcome of survival to ICU discharge.

Results

A total of 288 admission episodes were reviewed, of which 264 were included for analysis. Overall ICU mortality was 34.8%, and overall hospital mortality was 45.8%. The mean duration of ICU stay was 5.3 days.

The type of HM did not affect the outcome ($P = 0.87$), nor did the presence of relapsed/refractory disease ($P = 0.38$). Neutropenia ($P = 0.02$) and positive blood culture ($P = 0.002$) were associated with higher mortality. The use of RBC ($P = 0.58$) and platelet transfusions ($P = 0.10$) did not affect the outcome. Higher SOFA and APACHE II scores were both associated with higher rates of ICU mortality (both $P < 0.001$).

The 9 variables that were found to be significant with $P < 0.05$ were analyzed in a multivariable logistic regression model. APACHE II score ($P < 0.001$), use of mechanical ventilation ($P = 0.003$), use of vasopressor drugs ($P < 0.001$), and serum bilirubin ($P = 0.004$) were found to be independently associated with ICU mortality.

Conclusions

Physiological parameters and indicators of organ dysfunction at the point of ICU admission were predictors of ICU mortality. The type of HM and the presence of refractory disease did not have a significant effect on ICU outcome. This information can help determine which patients would benefit most from intensive care. The results also suggest that patients should not be denied ICU admission solely based on the status of their HM.

CS-41

Shortlisted for Poster Award Presentation

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Allogeneic Haematopoetic Cell Transplant For Adults with Philadelphia Chromosome Positive Acute Lymphoblastic Leukaemia in the Era of Tyrosine Kinas Inhibitors – A Comparative Analysis of Different Donor Sources

Background

Allogeneic haematopoietic cell transplantation (HCT) in first complete remission (CR1) remains the consolidation therapy of choice in patients with Philadelphia-positive acute lymphoblastic leukaemia (Ph+ ALL). In patients without a matched related donor (MRD), the risk and benefits of alternative donors, such as matched unrelated donors (MUD) or unrelated umbilical cord blood (UCB), remains to be determined.

Methods

We studied 55 patients undergoing first allogeneic HCT for Ph+ ALL between January 2005 and December 2016. The patients received transplantation using MRD (n=24), MUD (n=14) or 4-6/6 human leukocyte antigen (HLA) matched UCB (n=17) grafts, using either myeloablative (MAC, n=35) or reduced intensity conditioning (RIC, N=20) regimens.

Results

The overall (OS) and disease-free survival (DFS) at 10 years were 57% and 53% respectively, with no statistically significant difference for each donor type or type of conditioning regimen. The 3-year cumulative incidence of relapse and non-relapse mortality (NRM) was 22% (95% confidence interval (CI) 12%-32%) and 23% (95% CI 12%-35%), respectively. There were no relapses beyond 2 years. There was no statistically significant difference in relapse rates and NRM among the 3 donor types. The cumulative incidence of grade 2-4 acute and chronic graft-versus-host disease were 40% and 30%, respectively.

Conclusions

Our results support the use of UCB and MUD as a suitable alternative for Ph+ ALL patients without an available HLA-MRD, with modest NRM and good long-term leukemia-free survival.

CS-45

Shortlisted for Poster Award Presentation

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Ploidy by Conventional Karyotyping is an Important Prognostic Marker for Myeloma in the Era of R-ISS Staging

Background

The Revised International Staging System (R-ISS) staging system highlights the importance of Lactate Dehydrogenase (LDH), Fluorescence In Situ Hybridization (FISH) and the ISS for prognostication of multiple myeloma (MM) patients. As a result, the continued utility of conventional karyotyping, has been called into question.

Methods

A multi-centre study for newly diagnosed MM patients who received novel agent/s at induction from year 1999 at the National University Hospital, Singapore General Hospital and Peking University Institute of Hematology, was conducted. We evaluated the correlation between conventional karyotypic abnormalities to the overall survival (OS) for patients with different R-ISS stages.

Results

A total of 632 patients were evaluable. Karyotype significantly affected OS of patients with R-ISS stage I (N=88; p=0.007) and II (N=408; p=0.000) but not R-ISS Stage III (N=136; p =0.515). Patients with non-hyperdiploid MM did particularly badly.

In the multivariate analysis adjusting for the R-ISS stages, transplant status, age, novel agent/s used at induction, karyotypic abnormalities were still significantly associated with OS (p=0.000). In fact, by replacing FISH with karyotypic abnormalities, in the R-ISS system, we are able to similarly identify a high-risk population.

We proposed a new prognostic scoring system by incorporating karyotypic abnormalities in addition to the R-ISS staging system. In this R-ISS+K staging, patients can be divided into: Standard Risk (R-ISS stage I or R-ISS stage II with no non-hyperdiploid karyotype) and High Risk (R-ISS stage II with non-hyperdiploid karyotype or R-ISS stage III). Patients in the 2 groups had significantly different OS (median OS 92.1 versus 38.7 months, p=0.000).

Conclusions

Conventional karyotyping is an independent prognostic factor even in the setting of R-ISS. Ploidy by karyotyping can be incorporated into R-ISS staging to make a new staging system (R-ISS+K).

CS-46

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Presence of post induction minimal residual disease (MRD) is an independent predictor for relapse and is associated with inferior survival in acute myeloid leukemia (AML)

Background

AML is a heterogenous disease.Current risk stratification is based on cytogenetics and some molecular genetic markers at diagnosis.A significant proportion of AML patients have detectable MRD post induction.There is increasing evidence to support MRD as a significant prognostic factor on clinical outcome.Despite this, MRD status has yet to become an important factor in deciding on subsequent allogeneic stem cell transplant(allo-SCT). This study assessed the role MRD in predicting risk of relapse and survival rates.

Methods

All AML cases who underwent curative chemotherapy from year 2001 until 2015 were retrospectively identified. Clinical data was gathered from computerised patient data system.Baseline patients and disease characteristic were correlated with post induction MRD status.MRD status was assessed for its prognostic impact.

Results

275 patients underwent intensive chemotherapy. 64.6% achieved CR after induction chemotherapy.Among those who achieved CR, 35.6% have detectable MRD.The presenting WBC,LDH,time taken for neutrophil count or platelet count recovery after induction,molecular status did not correlate with MRD status.AML in adverse risk group appeared to have higher incidence of MRD+, 52.5% compared to 29.1% and 39.6% for favorable and intermediate risk respectively,(p=0.07).Post induction MRD level was associated with higher relapse risk (OR = 1.41) (95% CI: 1.84-1.08).In the multivariate analysis that include presenting WBC, LDH, BM blasts, risk group and MRD status, risk group and MRD status remain as the independent predictor for relapse.The 5-yr Leukemia free survival(LFS) was 47.2% and 66.1% for MRD+ and MRD- group respectively (p=0.003).Among those with MRD+ intermediate or adverse risk who did not undergo allo-SCT,the 5 yrs LFS was only 11.4% compared to allo-SCT group, 37.8% p=0.042.

Conclusions

Post induction MRD+ was associated with risk of relapse and reduced LFS.Allo-SCT may be able to abrogate the adverse outcome of MRD+ AML.

CS-47

Chin-Hin Ng, Benedict Yan, Christopher Ng, Wee-Joo Chng

Clinicopathology of Acute Myeloid Leukemia Harboring TP53 mutation

Background

TP53 gene is a tumor suppressor gene located on the short arm of chromosome 17. TP53 plays a pivotal role in maintaining genomic stability in response to DNA damage. It is mutated over 50% of human cancer. TP53 mutation (TP53mut) is commonly associated with therapy-related AML and complex karyotype. The incidence of TP53 mutation was between 5-10% in de novo AML. This study described the clinicopathologic features of TP53mut AML and their clinical outcome in an Asian cohort.

Method

158 consecutively cell-banked marrow samples of AML were tested for TP53 mutation using NGS Trusight Myeloid Genes panel on a MiSeq Illumina platform. Baseline disease characteristic and clinical outcomes were retrospectively collected with approval granted by institutional review board.

Results

9/158 had TP53 mutation (5.7%). 6/9 of TP53mut AML was associated with complex karyotype ($p<0.001$). The remaining 3 cases were two APML and one normal cytogenetics. TP53 mutation was mutually exclusive with the FLT3 mutation. Two cases had a concomitant NPM1 mutation and another two had ASXL1 mutations. TP53mut AML appeared to be associated with TET2 mutation (3/9, 33.3%) compared to 9.4% of the TP53wt ($p=0.058$). TP53mut AML had a lower CR rate compared to TP53wt (28.6% vs 84.3%, $p=0.003$). Only two cases achieved CR, one was an APML who remained in continuous remission after 4 years. The other case achieved CR after allogeneic transplant but relapsed 8 months later. TP53mut AML was significantly associated with inferior OS compared to TP53wt ($p=0.001$). Median OS was 1.4 months (95%CI:0.2-2.6) and 102.2 months (95%CI:27.5-176.9) respectively. It remains an independent predictor of OS in multivariate analysis that includes cytogenetic risk, WBC, LDH and BM blasts (HR 7.8, 95%CI:1.8-33.5, $p=0.005$).

Conclusion

Our results confirmed the extremely dismal prognosis of TP53mut AML. The significance of its association with TET2 mutation requires further exploration in a larger study cohort.

CS-52

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Autologous Haematopoietic Stem Cell Transplantation using BEAM +/- Rituximab for Relapsed Diffuse Large B Cell Lymphoma in the Rituximab Era – Ten Year Follow-Up of Single Transplant Center in Singapore

Introduction

High dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) has shown to improve outcome in patients with relapsed/refractory diffuse large B cell lymphoma (DLBCL). In the Rituximab era, it remains unclear whether addition of Rituximab to standard HDT regimen BEAM provides any additional benefit.

Methods

We studied 63 patients HDT using BEAM (n=27) or R-BEAM (n=36) followed by ASCT for relapsed/refractory DLBCL since 2002. All patients who received CHOP (n=15) +/- Rituximab (n=48) as first line therapy and who received ≤ 2 lines of salvage chemotherapy before ASCT.

Results

22 (81 %) patients in BEAM group and all the patients (100%) in R-BEAM group received Rituximab based salvage chemotherapy prior to ASCT. The 10-year overall survival (OS) was 71% and event-free survival (OS) was 67% for the whole cohort. R-CHOP induced patients did not fare any worst after ASCT than CHOP induced patients (10 year OS 73 vs. 68 %; p=0.91). There was a trend towards better survival in patients with pre-transplant disease free interval (DFI) > 12 months compared to those with DFI <12 months/refractory disease (10 year OS 76% vs. 69 %; p=0.44). There was no significant difference in haematopoeitic recovery between R-BEAM and BEAM. Ten year OS (67% R-BEAM vs. 77% BEAM, p= 0.38) and EFS (65% R-BEAM vs. 73% BEAM, p= 0.28) were also comparable between both groups.

Conclusion

HDT with BEAM and ASCT should continue to be offered to patients who respond to salvage chemotherapy with the expectation that they fare no worse than patients who do not receive Rituximab in the induction chemotherapy. Addition of Rituximab onto the standard BEAM for HDT and ASCT does not result in improved outcome in our study. Prior use of Rituximab during first-line or salvage therapy in most of the patients of BEAM group might have negated the beneficial effect of R-BEAM over BEAM.

CS-58

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Primary Mediastinal B cell lymphoma (PMBCL): Optimal induction chemotherapy strategies and prognostic factor analysis in 83 consecutive patients treated in 2 major cancer centers in Singapore between 2001 – 2016

Background

PMBCL is a distinct clinico-pathological subtype of large B-cell lymphoma with unclear prognostic factors, and limited clinical data especially in the Asian population. Optimal treatment as yet remains undefined.

Methods

We studied 83 consecutive patients with newly diagnosed PMBCL in 2 national cancer centers in Singapore, treated betweenJan2001 – Dec 2016: Chemotherapy regimens received included R-CHOP (n=42), dose adjusted (DA) R-EPOCH (n= 36) and others (n=3). 26 (31%) patients also received RT.

Results

The median age of the patients was 28 years (range 1-72) and the majority had stage I-II disease (75%) and bulky disease (59%). With a median follow up of 41months (range, 0.2-188 months) for surviving patients, overall (OS) and progression-free (PFS) survival at 10 years for the entire cohort were 95% and 81% respectively. On univariate analysis, there were no factors (including age, gender, LDH, bulky disease, disease stage or age adjusted IPI) that were predictive for PFS or OS. Outcomes were compared between the group receiving R-CHOP +/- RT (n= 42) and the group receiving DA R-EPOCH (n=36). Both groups were similar in baseline disease characteristics. Overall, 52% (n=22/42) of patients in R-CHOP group and 8% (n=3/36) in REPOCH group had RT. 10 year OS for patients receiving R-CHOP +/- RT and DA R-EPOCH were 97 %, 93 %, and of PFS were 88 %, 91 %, respectively; these were not significantly different. In subgroup analysis of the patients with bulky disease (n=46), patients receiving RCHOP alone (n=12) had worse outcomes compared to those receiving RCHOP + RT (n=12) or R-EPOCH (n=22), with 5 year PFS of 48 %, 100 % and 91%, respectively (p=0.02).

Conclusion

Both R-CHOP +/- RT and R-EPOCH are associated with excellent outcomes in patients with PMBCL in the rituximab era. In patients with bulky disease, the use of DA R-EPOCH may be preferable as it allows omission of RT without reduction in efficacy.

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Shortlisted for Poster Award Presentation

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Identification of novel putative fusions in multiple myeloma using a targeted RNAseq panel

Background

Multiple Myeloma (MM) is a genetically complex disease. The classical mutational spectrum which includes recurrent chromosomal and gene-level mutations is well-characterized. Recurrent translocations such as t(11;14), t(4;14) and t(14;16) are routinely detected by FISH for clinical management. However, conventional karyotyping is informative in only about 40% of cases due to low proliferation rate of the malignant plasma cells, hence spectrum of fusions in myeloma is not well studied. We therefore employed a targeted RNA-sequencing panel to identify novel putative fusions in a local cohort of MM.

Methods

Targeted RNA-sequencing was performed on 24 patient samples using Illumina® TruSight® RNA Pan-Cancer Panel (1385 genes). Fusion calls were generated from the Illumina® RNA-Sequencing Alignment software (Version 1.0.0), a pipeline comprising aligner (STAR) and fusion caller (Manta). Of these, 21 samples had conventional cytogenetics and FISH performed. Targeted RNA-sequencing fusion call results were compared against those obtained from FISH.

Results

10 putative high-confidence fusions were identified by the RNA Pan-Cancer Panel. 4 of these (MAP2K4/MAP2K4P1) are likely to be spurious, secondary to misalignment of reads to a pseudogene. 2 pairs of fusions involve genes that may play a biological role in MM genesis. For one of the fusion pair HGF/CACNA2D1, HGF is a growth factor that impacts myeloma growth and survival through HGF/Met signaling pathway. FISH detected 10 chromosomal abnormalities comprising of t(11;14), t(4;14), t(14;16), and 17p13 deletion, which were not identified by the panel.

Conclusions

The identification of putative novel fusions offer insights into the biology of MM and might have clinical relevance. Further technical and functional studies are necessary to confirm and characterize these novel putative translocations and to explore the use of different fusion callers for identifying the recurrent chromosomal aberrations in MM.