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IRANIAN SOCIETY OF MEDICAL ONCOLOGY AND HEMATOLOGY
ISMOH

Ph Positive ALL in Post TKI era

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Ph Positive ALL

1) What is the best remission induction regimen?

2) What is the significance of molecular remission?

3) What is the best TKI?

4) Is Allogenic SCT necessary?

5) Is maintenance with TKI necessary?

Introduction

- Ph+ ALL is the most common chromosomal abnormality in adult ALL , accounting for 20 %–30 % of all cases and more than 50 % in the elderly
- In the pre-TKI era, the prognosis of this disease was very dismal, overall survival (OS) ranging from 8% to 22 % at 5 years for patients solely treated with intensive chemotherapy versus a long-term survival of 40 % when treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT)

Introduction

- The introduction of TKIs has changed dramatically outcomes of adult patients with Ph+ ALL, not only improving complete remission (CR) rates, duration, and depth of remissions but also increasing the OS of adult patients with Ph+ ALL, mainly due to the increased rates of allo-HSCT. The 5-year OS is approximately 50 % with allo-HSCT in the TKIs era

Intensive Chemotherapy with TKI

TKI	N	Median age, years [range]	CR rate, %	Induction mortality, %	Overall CMR rate, %	HSCT rate, %	RFS rate, %	OS rate, %
Intensive chemotherapy + TKI								
Imatinib	54	51 [17-84]	93	2	45	30	43 (5-year)	43 (5-year)
Imatinib	169	42 [16-64]	92	5	NR	72	50 (4-year)	38 (4-year)
Dasatinib	72	55 [21-80]	96	4	60	17	44 (5-year)	46 (5-year)
Nilotinib	90	47 [17-71]	91	9	86	70	72 (2-year)	72 (2-year)
Ponatinib	86	46 [21-80]	100	0	86	21	84 (3-year)	78 (3-year)

Intensive Chemotherapy with TKI

- Addition of imatinib to intensive chemotherapy improved CR rates to 95% and long term OS rates to 40-50% which compared very favorably to the historical long term OS of less than 10-20% in the pre TKI era.
- Despite the high efficacy of this combination, for patients with Philadelphia chromosome- positive adult acute lymphoblastic leukaemia, when second-generation tyrosine-kinase inhibitors are used, the 3-year event-free survival is 40% and overall survival is 60%, at best.

Intensive Chemotherapy with TKI

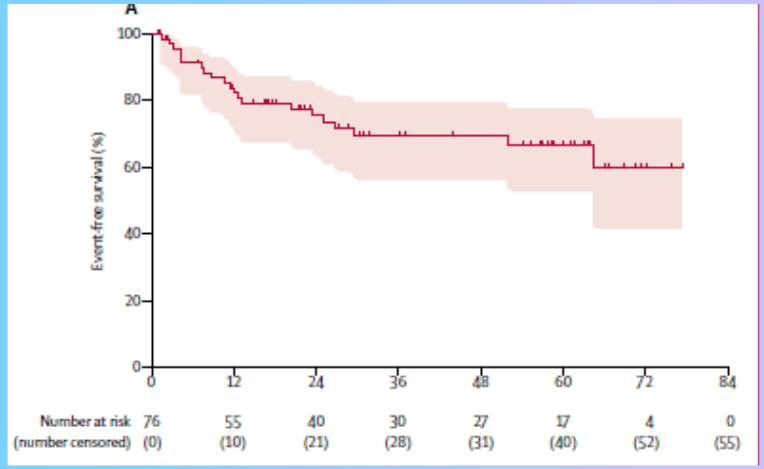
- T315I mutations of the ABL1 kinase domain have been described in up to 75% of patients who relapse after treatment with first- or second-generation TKIs This has led to interest in using ponatinib, a third generation TKI with high potency and activity against this common resistance mutation

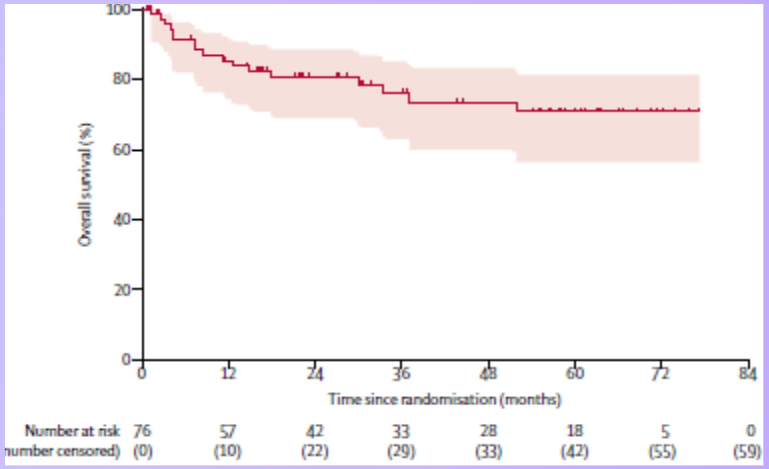
Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study

Elias Jabbour, Nicholas J Short, Farhad Ravandi, Xuelin Huang, Naval Daver, Courtney D DiNardo, Marina Konopleva, Naveen Pemmaraju, William Wierda, Guillermo Garcia-Manero, Koji Sasaki, Jorge Cortes, Rebecca Garris, Joseph D Khoury, Jeffrey Jorgensen, Nitin Jain, Joie Alvarez, Susan O'Brien, Hagop Kantarjian

Intensive Chemotherapy with TKI

- 3-year event-free survival of 70%
- 3 -year overall survival of 76%





Intensive Chemotherapy with TKI

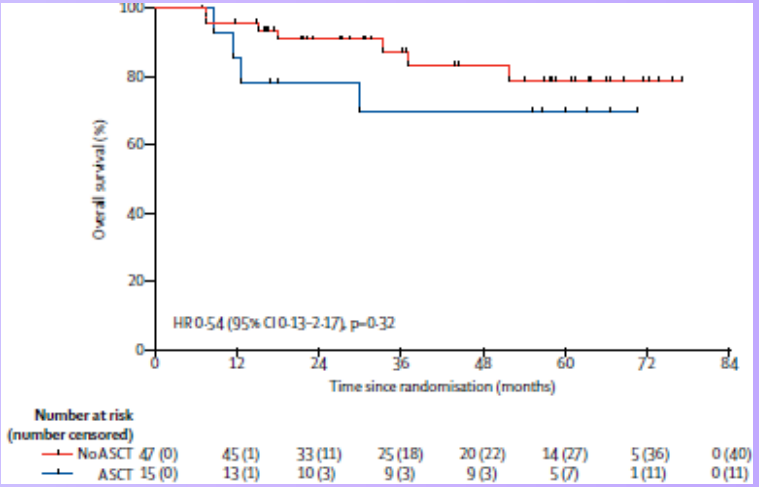
- The 3-month CMR rate was 74%, and the cumulative CMR rate was 84%. Only 18 patients (21%) underwent HSCT in CR1.

- With a median follow-up of 44 months, 71% of patients remain alive in remission, and only 3 relapses occurred while on ponatinib.

- The 3-year overall survival for patients with a complete molecular response at 3 months follow-up was 81% (95% CI 64–91), and for patients without at the same time point was 72% (41–88; p=0.27). In a post-hoc analysis, 3-year overall survival did not differ between patients aged 59 years or younger and those aged 60 years or older (p=0.90)

Intensive Chemotherapy with TKI

- The 3-year overall survival was 70% (95% CI 38–88) for patients who received allogenic stem cell transplantation and 87%(72–95) for patients who did not receive stem cell transplantation(hazard ratio [HR]=0.54, 95% CI 0 · 13–2 · 17; p=0.32).



Comparative Efficacy of Ponatinib versus Earlier-Generation Tyrosine Kinase Inhibitors for Front-line Treatment of Newly Diagnosed Philadelphia-positive Acute Lymphoblastic Leukemia

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Ponatinib v/s earlier generation TKIs

- The percentage of patients achieving CMR was higher with combination chemotherapy plus ponatinib(79%)than the pooled percentage of patients achieving CMR with combination chemotherapy plus earlier-generation TKIs (34%). Higher OS was observed with ponatinib compared to the pooled OS for earlier-generation TKIs (2-year: 83% versus 58%; 3-year: 79% versus 50%).

- Odds ratios (OR) for ponatinib versus earlier-generation TKIs were 6.09(95% CI: 1.16-31.90, p=0.034) for CMR, 3.70 (95% CI: 0.93-14.73, p=0.062) for 2-year OS, and 4.49(95% CI: 1.00-20.13, p=0.050) for 3-year OS.

Lower Intensity chemotherapy + TKI

- Since the incidence of Ph+ALL increases with age, the potent activity of TKIs and intolerance to intensive chemotherapy for older patients leads to the investigation of TKIs plus lower-intensity induction chemotherapy or steroid only for adult patients with Ph+ ALL.
- Thereafter, the que CR rates ranged from 94 % to 100 %, and among the younger group, more than 50 % of patients proceeded to allo-HSCT with a 5-year OS rate of over 50 % .
- Stion of whether intensive chemotherapy during the induction or consolidation phases is necessary for adults fit for allo-HSCT is raised.

Lower Intensity chemotherapy + TKI

Outcomes of TKIs combined with lower-intensity induction therapy followed by allo-HSCT for adult patients with Ph^+ ALL.

Reference	N	Median age (range)	Induction and consolidation therapy	CR (%)	ED (N)	CMR (%)	Allo-SCT (CR1, %)	OS #(%)	DFS #(%)	CIR #(%)
Ribera et al [13]	29	38 (mean)	PDN/VCR/DNR + I→MTX/Ara-C/VP-16/MP + I	29 (100)	0	77 (Cos)	26 (90)	NA	63 (2 yrs)	15 (2 yrs)
Chalandon et al [9]	135	49 (18–59)	VCR/DXM + I→MTX + Ara-C + I	133 (99)	1	29 (Cos)	82 (62)	57 (5 yrs)	50 (5 yrs)	18.7 (5 yrs)
Chiaretti et al [14]	51	46 (17–60)	PDN + I→HAM + I	47 (96)	0	3 (50d)	20 (43)	49 (5 yrs) *	46 (5 yrs) *	25 (5 yrs)
Chalandon et al [15]	60	47 (18–59)	VCR/DXM + N→MTX ± Ara-C + N	59 (98)	1	NA	31 (53)	96 (1 yrs) *	85 (1 yrs) *	NA
Ottmann et al [16]	72	66 (55–85)	VCR/DEX + N→MTX + AraC + N	68 (94)	1	58 (Cos)	24 (35)	61 (4 yrs)	NA	32 (4 yrs)
Foà et al [17]	53	54 (24–77)	PDN + D→NA	53 (100)	0	15 (85d)	18 (34)	69 (20 mos)	51 (20 mos)	31 (20 mos)
Rousselot et al [18]	71	69 (55–83)	VCR/DEX + D→MTX + Ara-C + D	67 (94)	3	24 (Cos)	7 (10)	36 (5 yrs) *	28 (5 yrs) *	57 (5 yrs) *
Wieduwilt et al [19]	64	60 (22–87)	DEX + D→CTX/DNR/VCR/DEX + D	62 (97)	0	NA	20 (32)	75 (3 yrs)	55 (3 yrs)	25 (3 yrs)
Li et al [20]	13	41 (16–73)	PDN + D→PDN + D or CT	13 (100)	0	15 (28d)	6 (46)	90.9 (2 yrs) *	45.5 (2 yrs) *	NA
Chiaretti et al [21]	60	42 (19–59)	PDN + D→Clopha + CTX + D	58 (97)	0	18 (85d)	22 (38)	56 (57.4 mos) *	47 (57.4 mos) *	30 (57.4 mos) *
Foà et al [22]	63	54 (24–82)	Steroids + D→D + B	62 (98)	1	60 (Cos)	24 (39)	98 (18 mos) *	88 (18 mos) *	6 (18 mos) *

Lower Intensity chemotherapy + TKI

CLINICAL TRIALS AND OBSERVATIONS

Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia

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Lower Intensity chemotherapy + TKI

In this study, we randomly compared high doses of the tyrosine kinase inhibitor imatinib combined with reduced-intensity chemotherapy (arm A) to standard imatinib/hyperCVAD (cyclophosphamide/vincristine/doxorubicin/dexamethasone) therapy (arm B) in 268 adults (median age, 47 years) with Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL). The primary objective was the major molecular response (MMolR) rate after cycle 2, patients being then eligible for allogeneic stem cell transplantation (SCT) if they had a donor, or autologous SCT if in MMolR and no donor. With

Lower Intensity chemotherapy + TKI

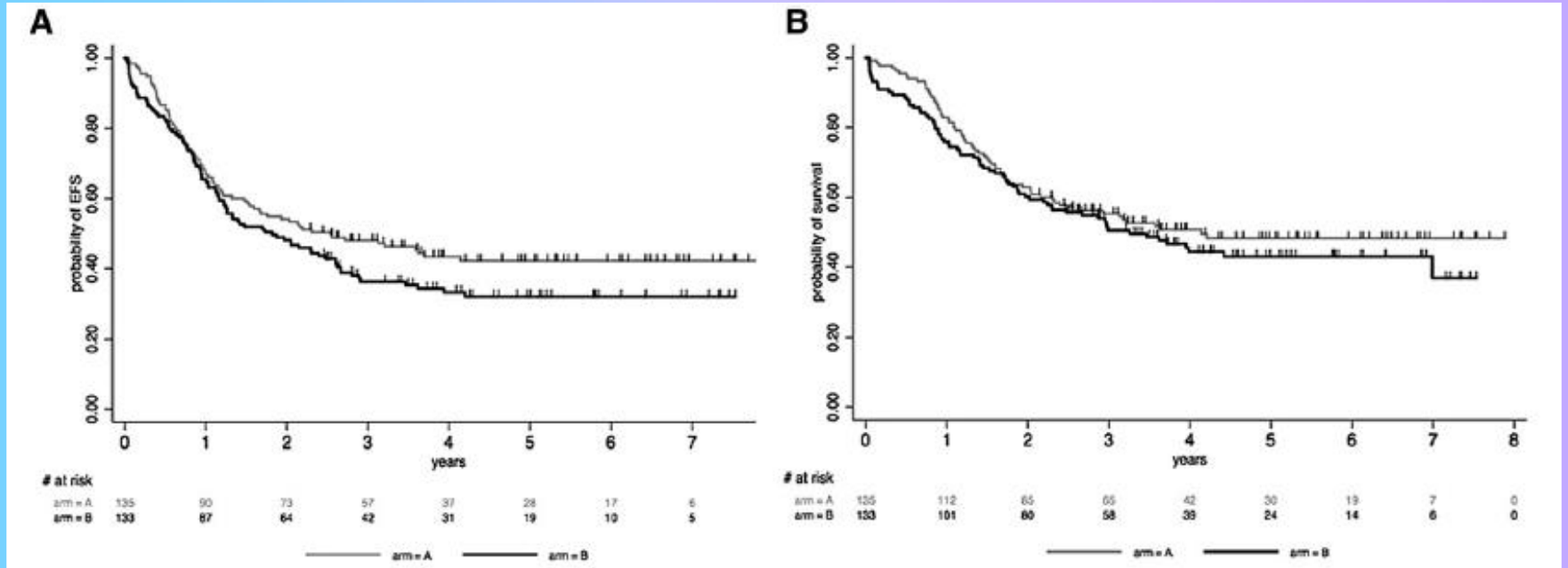


Figure 1. Outcome by randomization arm. (A) EFS by randomization arm. At 5 years, the EFS rate was estimated at 32.1% (95% CI, 24.0-40.4) in arm B vs 42.2% (95% CI, 33.5-50.6) in arm A ($P = .13$). (B) OS by randomization arm. At 5 years, the OS rate was estimated at 43.0% (95% CI, 33.9-51.7) in arm B vs 48.3% (95% CI, 39.2-56.8) in arm A ($P = .37$).

Lower Intensity chemotherapy + TKI

- **Results:(GRAALL)**
- **With** fewer induction deaths, the complete remission (CR) rate was higher in arm A than in arm B (98% vs 91%; P=0.006), whereas the CMR rates were similar after the second cycle(28.6% versus 22.6%). With a median follow-up of 4.8 years, 5-year event-free survival and overall survival (OS) rates were estimated at 37.1% and 45.6%, respectively, without difference between the arms.
- **The** 5-year RFS and OS of allo-SCT were 50% and 57% respectively in the reduced intensity induction cohort, without statistically significant difference between the two groups

Lower Intensity chemotherapy + TKI

- Ongoing phase III study to answer whether lower-intensity chemotherapy with nilotinib during induction and consolidation phases**(GRAAPH-2014 trial)** followed by allo-HSCT would lead to better outcomes among newly diagnosed adults who were candidates for allo-HSCT and 60 adult patients with a median age of 47 years (range, 18- 59 years) were enrolled.
- After cycle 1, the CR rate was 98 %, and one death was caused by sepsis while the cumulative major molecular remission (MMR) rate after 4 cycles was 93 % (38/41). 73 percent of patients were able to proceed to allo-HSCT in CR1. With a median follow-up of 14 months, the estimation for the 1-year progression-free survival (PFS) and OS were 85 % and 96 % respectively. However, they didn’t report the rate of CMR and 5 out of 7 patients relapsed with T315I mutation during therapy

Steroids + TKI

- Several trials also evaluated the frontline combination of TKIs (most at a higher dose) with steroids in elderly frail patients with excellent CR rates and minimal toxicity .
- However, deep responses were, not unexpectedly, rarely attained, remissions were short, and relapses were common resulting in poor long-term survival. The rates of CMR appear to be higher with successive generations of TKIs (e.g., 46% with ponatinib 18% with dasatinib, and 4% with imatinib)
- The major challenges of de-intensified chemotherapy are relatively lower CMR rates and the risk of inducing TKI resistance. CMR rates ranged from 3% to 18 % after induction with imatinib or dasatinib combined with lower-intensity induction therapy, while consolidation with intensive chemotherapy increased CMR rates up to 77 %

Conclusion

- There is no consensus on how the intensity of chemotherapy therapy is appropriate for those proceeding to allo-HSCT and chemotherapy may play a role in constraining the emerge of TKIs-resistant mutants.

- Nevertheless, the combination of a more potent TKI with lower-intensity induction therapy and deferred intensive chemotherapy as consolidation is a valid choice to reduce treatment-related mortalities among patients with older age or comorbidities at diagnosis. In the near future, TKIs plus novel antibodies may bring us to a chemotherapy-free era.

Significance of molecular remission in Ph+ ALL

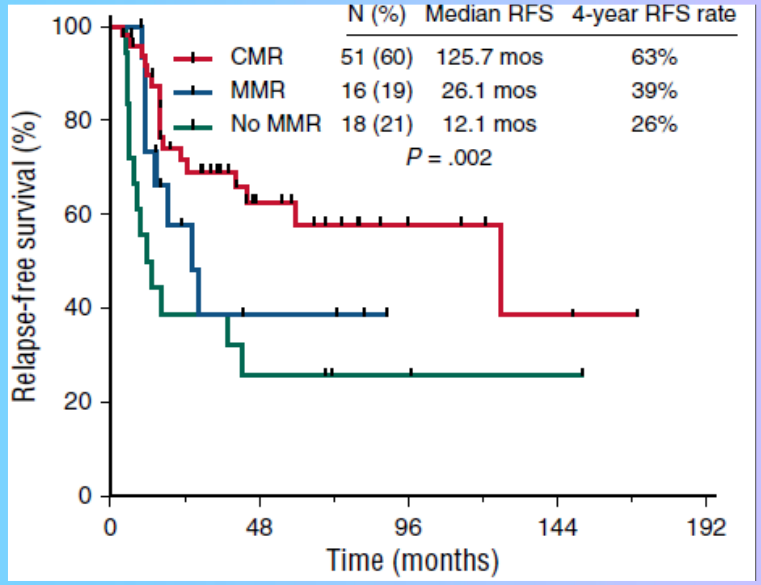
- Chemotherapy alone could transiently induce an MRD-negative status. Response to selected chemotherapy agents (anthracyclines) and synergistic effects of TKI-chemotherapy combinations were reported . 38% MRD negativity have been reported after two intensive chemotherapy courses

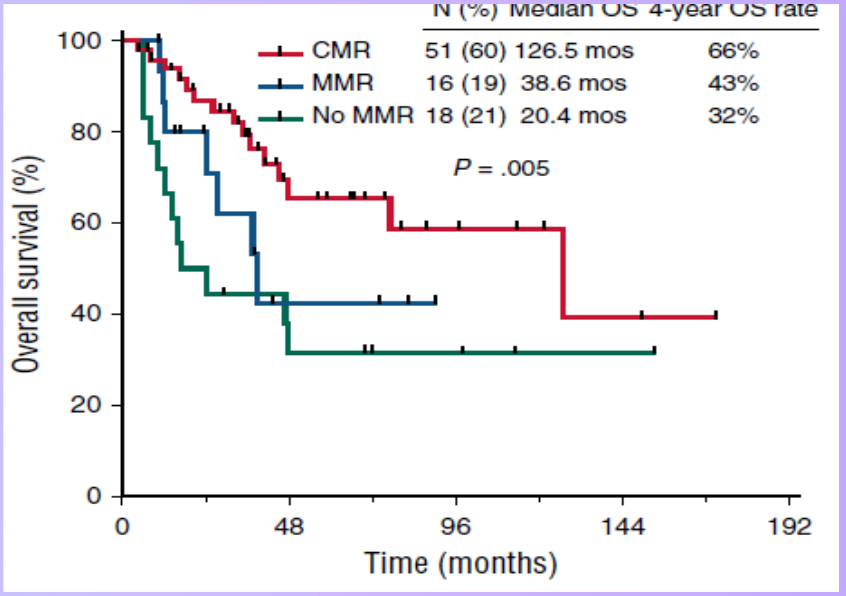
- These facts point to the usefulness of associated chemotherapy, at least in selected patients who have no access to innovative drugs and/or display clinical or molecular TKI resistance

- Post-induction MRD results from TKI-based studies were quite variable, depending on TKI type and associated chemotherapy

CMR in 3 months

- At 3 months, achievement of CMR vs response less than CMR was associated with longer median OS (127 vs 38 months, respectively; P = 0.009) and RFS (126 vs 18 months, respectively; P = 0.007).





Significance of molecular remission in Ph+ ALL

- First, imatinib or dasatinib with or without chemotherapy yielded favorable early MRD responses (CMR, MMR) in the 20% range, with no differences between intensive and non-intensive chemotherapy

- Nilotinib In combination with chemotherapy of variable intensity, early CMR rates were close to 60%, and MMR rates close to 80%

- The best MRD results were reported with ponatinib, with CMR rates of 60–80% (the higher figure in association with intensive chemotherapy) and an outstanding MMR rate of 97% in one study

Allogenic SCT

- In the TKI era, an allogeneic SCT can be performed in 45–80% of CHR patients , representing a major contribution to an overall survival of 35–55% at 2–5 years, and up to 60–70% among allografted patients

- The current standard treatment paradigm for adult Ph+ ALL, consisting of a TKI-based induction/consolidation followed by an allograft

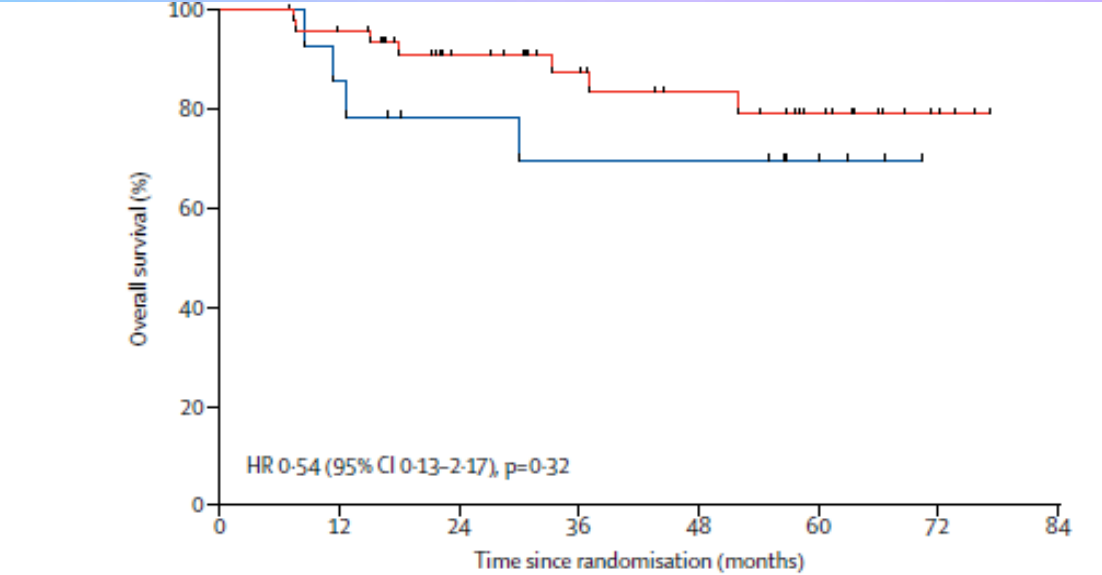
- Due to significant mortality and morbidity associated with allogenic SCT , and high relapse rate with autologous SCT leads to a transplant free strategy

Allogenic SCT

- Many of the trials reported survival rates around 30–50% at 2–5 years in non-SCT patients, with minimal or statistically non-significant differences as compared to SCT-treated patients .

- The most striking example was the ponatinib/ chemotherapy phase 2 trial from the M.D. Anderson Hospital. In that study, very recently updated, the 3-year overall survival was 70% for allografted patients (n = 15, TRM 20%) compared to 87% for the 61 patients who continued on study drugs after the achievement of a major/ complete MRD response.

Allogenic SCT



Study (author, ref.)	No. of patients	TKI-based therapy	Treatment outcome (%)						
			General	SCT			No SCT		
				No.	Outcome	TRM	No.	Outcome	*P* (vs. SCT)
Pfeifer (2010) [63]	247	IM/CT	40–50 (OS, 4 years)	180	57 (OS, 3 years) 72 (DFS)	21–26	–	14 (OS, 3 years)	NR
Bassan (2010) [64]	53	IM/CT	38 (OS, 5 years) 39 (DFS)	34	46 (DFS, 5 years)	17	19	30 (OS, 2 years)	0.019 (DFS)
Ribera (2012) [65]	56	IM/CT	37–63 (EFS, 2 years)	32	NR	31	24	NR	NR
Thyagu (2012) [66]	30	IM/CT	53 (OS, 3 years) 50 (EFS)	16	56 (OS, 3 years) 70 (EFS)	37.5	14	50 (OS, 3 years) 45 (EFS, 3 years)	0.34 (OS) 0.51 (DFS)
Fielding (2014) [67]	161	IM/CT	38 (OS, 4 years) 50 (DFS) 33 (EFS)	93	52 (OS, 4 years) 72 (DFS) 49 (EFS)	NR	44	19 (OS, 4 years) 14 (DFS) 14 (EFS)	NR
Chalandon (2015) [68]	254	IM/CT	45.6 (OS, 5 years) 37.1 (EFS)	148	56.7 (OS, 5 years) 48.3 (DFS)	25.8	106	35 (OS, 5 years) 28 (DFS)	0.02 (OS) 0.03 (DFS)
Daver (2015) [69]	39	IM/CT	43 (OS. 5 years) 43 (DFS)	16	63 (DFS, 5 years)	NR	23	43 (DFS, 5 years)	0.52 (DFS)
Lim (2015) [70]	82	IM/CT	39(OS, 5 years) 33 (DFS)	56	53 (OS, 5 years) 43 (DFS)	30	26	NR	NR
Chiaretti (2016) [72]	47	IM/CT	48.8 (OS, 5 years) 45.5 (DFS, 5 years)	23	NR	13	24	NR	0.03 (OS)
Wang (2018) [71]	136	IM/CT	69.2 (OS, 4 years) 61 (DFS)	77	82.6 (OS, 4 years) 71.3 (DFS)	10	56	45.6 (OS~4 years) 43.9 (DFS)	< 0.001 (OS, DFS)
Chiaretti (2015) [58]	60	DAS/CT	58 (OS, 3 years) 49 (DFS, 3 years)	NR	NR	NR	NR	NR	NR
Ravandi (2016) [74]	83	DAS/CT	69 (OS, 3 years) 62 (DFS) 55 (EFS)	41	76 (DFS, 3 years)	0	53*	56 (OS, 3 years) 51 (DFS)	0.037 (OS) 0.038 (DFS)
Kim (2015) [73]	82	NIL/CT	72 (OS, 2 years)	57	78 (DFS, 2 years)	19	25	49 (DFS, 2 years)	0.045 (DFS)
Ottmann (2018) [78]	68	NIL/CT	47 (OS, 4 years) 42 (EFS)	24	61 (OS, 4 years)	25	44	39 (OS, 4 years)	NS
Jabbour (2018) [75]	76	PON/CT	71 (OS, 5 years) 83 (DFS, 3 years) 67 (EFS)	15	70 (OS, 3 years)	20	61	87 (OS, 3 years)	0.32 (OS)

Allogenic SCT

- A Chinese study reported an excellent 84% disease-free survival without allogeneic SCT in low-risk patients identified by a presenting leukocyte count < 30 × 109/l and a good MRD response (≥ 3 logs)

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ORIGINAL ARTICLE

Cancer Science WILEY

Tyrosine kinase inhibitor prophylaxis after transplant for Philadelphia chromosome-positive acute lymphoblastic leukemia

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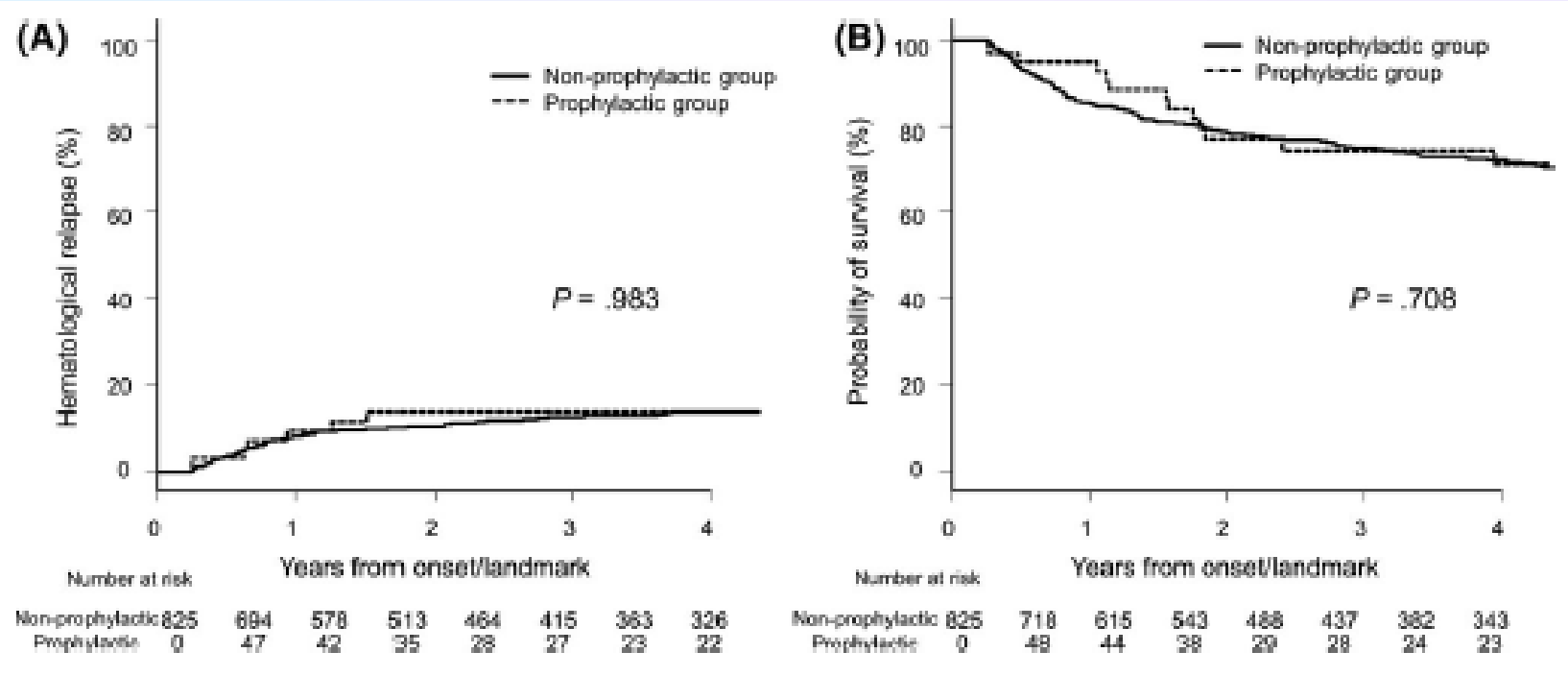
On behalf of the Adult Acute Lymphoblastic Leukemia Working Group of the Japan Society for Hematopoietic Cell Transplantation

Maintenance Therapy

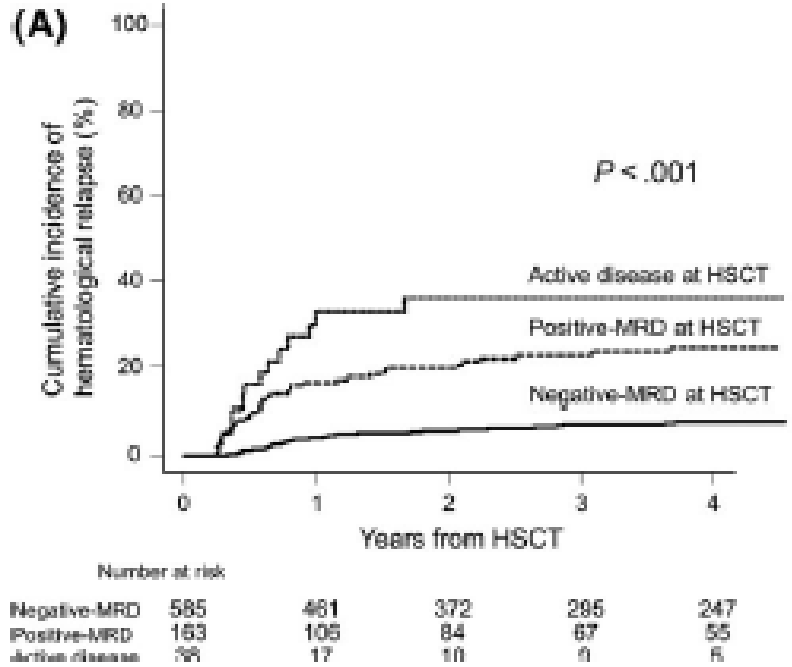


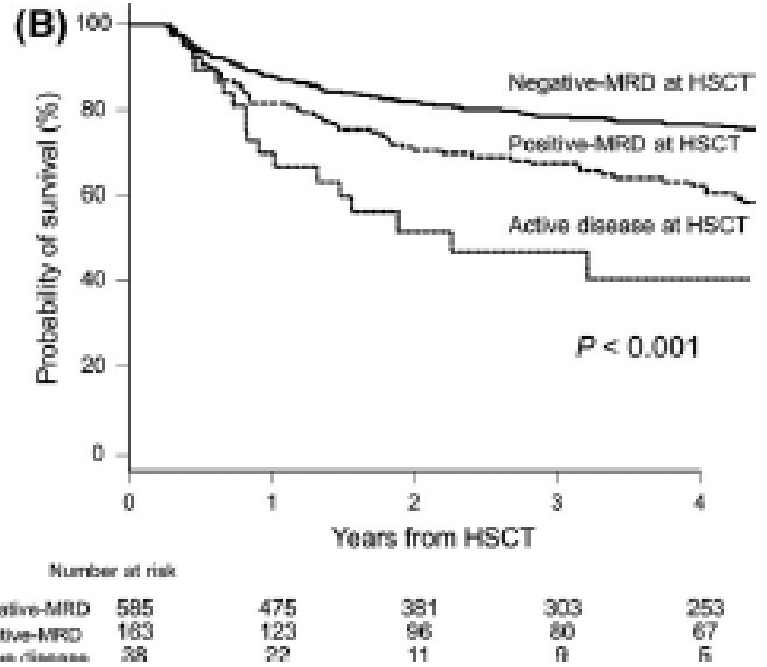
Maintenance Therapy

- Four-year cumulative incidences of hematological relapse without TKI prophylaxis (n = 800) were 12.6% (95% CI, 10.2%-15.1%). Multivariate analysis showed that disease status at HSCT was the sole independent risk factor for hematological relapse (HR, 3.58; 95% CI, 2.30-5.57; $P < 0.001$ for positive-MRD with CR, and HR, 6.13; 95% CI, 3.12-12.04; $P < 0.001$ for active disease).

- TKI prophylaxis as a time-dependent covariate did not significantly affect hematological relapse in a multivariate analysis (HR, 0.69; 95% CI, 0.30-1.59; $P = 0.384$).

Maintenance Therapy





Maintenance Therapy

- Cumulative incidence of hematological relapse at 4 years was 7.8% (95% CI, 5.7%-10.4%) for negative-MRD with CR at HSCT, 24.4% (95% CI, 17.8%-31.5%) for positive-MRD with CR at HSCT, and 36.3% (95% CI, 20.6%-52.2%) for active disease at HSCT.

- Probability of overall survival at 4 years was 76.5% (95% CI, 72.5%-80.0%) for negative-MRD with CR at HSCT, 62.2% (95% CI, 53.7%-69.7%) for positive-MRD with CR at HSCT, and 40.2% (95% CI, 20.7%-58.9%) for active disease at HSCT

Maintenance Therapy

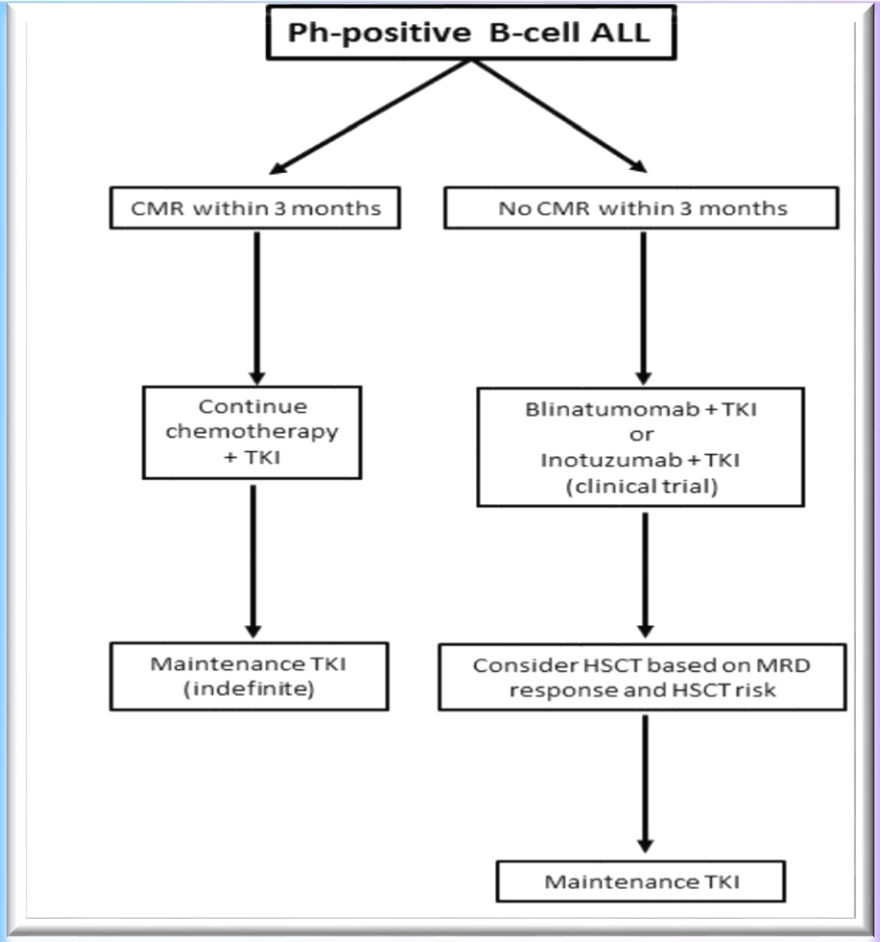
- Only one randomized prospective trial comparing the effect of prophylactic imatinib with preemptive imatinib therapy of adult Ph+ ALL patients in CR1 after allo-HSCT. They reported that the prophylactic group had a longer duration of MRD negativity (26.5 months versus 6.8 months; P = 0.065), a lower RR (40 % versus 69 %; P = 0.046), and a comparable 5-year OS (80 % versus 74.5 %).

- However, they also demonstrated that early detection (＜100 days) or high MRD level (＞10- 3) after transplantation was associated with limited benefit from intervention with imatinib

Maintenance Therapy

- According to tolerance and mutation status pre- or post-HSCT, prophylactic maintenance therapy with a sensitive TKI is an effective method to prevent relapse for those with positive-MRD or active disease before transplantation while a preemptive strategy could be considered for those with negative-MRD before transplantation

- An unsolved issue is the duration of this maintenance therapy because there is a reluctance of patients and physicians to skip them in patients with sustained molecular response and good TKI tolerability. The EBM statement recommends one year of continuous MRD negativity for TKI removal. However, as relapses until three years after alloHSCT are being observed, it seems more logical to remove TKIs at least from this moment


Ph-positive B-cell ALL
CMR within 3 months
No CMR within 3 months
Continue chemotherapy + TKI
Blinatumomab + TKI or Inotuzumab + TKI (clinical trial)
Maintenance TKI (indefinite)
Consider HSCT based on MRD response and HSCT risk
Maintenance TKI

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