高齢者DLBCLの治療戦略

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第14回中四リンパ腫カンファレンス
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日本大学

自己紹介

2007年	•血液専門医 •日本成人白血病治療共同研究グループ(JALSG)　支持療法委員
2008年	•JSCT研究会「末梢T細胞リンパ腫に対する自家および同種造血幹細胞移植の比較検討：日韓共同研究」 施設調査責任医師 •悪性リンパ腫治療研究会「未治療マントル細胞リンパ腫に対する化学療法および自家末梢血幹細胞移植」主任調査責任医師 •日本大学医学部内科学系血液膠原病内科　助教（がんプロ）
2009年	•NK腫瘍研究会「NK細胞腫瘍および関連T細胞腫瘍に関する多施設共同工法視的研究」 施設調査責任医師 •日本大学医学部附属板橋病院　腫瘍センター運営協議会　協議員
2010年	•がん薬物療法専門医 （海外学会派遣事業） •造血器腫瘍領域におけるMRSA感染症に対するarbekacinのPK-PD理論を用いた有用性の検討　代表責任研究者
2011年	•再発・難治性びまん性大細胞型B細胞リンパ腫に対するRituximab併用IDEA療法の第Ⅱ相臨床試験　施設責任医師

Agenda

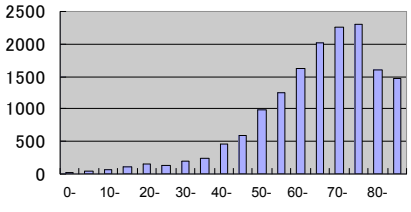
- Issues about elderly DLBCL
- Selecting Fit/Unfit patients
- Strategies for High/Low-risk patients
- Dose modification
- Alternates for R-CHOP
- Unfit/Refractory Patients
- Future directions

- From standardization to individualization -

高齢者の定義

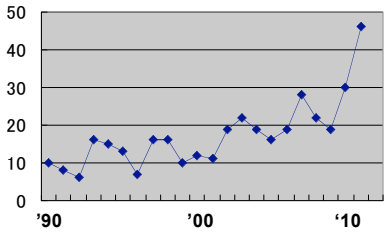
- 一般に決まったものは無い
- WHOでは「65歳以上」と定義
- 多くの臨床研究で習慣的に採用される
  ⇒生物学的根拠に乏しい
  ⇒同年齢でも臓器能の個人差は大きい

悪性リンパ腫の年齢階級別罹患者数



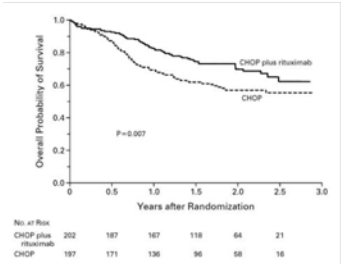
国立がんセンターがん対策情報センター
地域がん登録全国推計によるがん罹患データ(2002年)より

高齢者リンパ腫に関する研究



PubMed search: (elderly[Title]) AND lymphoma[Title]

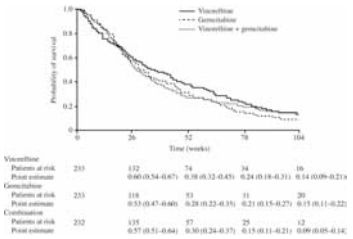
R-CHOP: the “Gold Standard”



Eligibility:
Age 60 - 80
Stage II - IV
PS 0 - 2

Coiffer et al. N Engl J Med 2002; 346: 235-42.

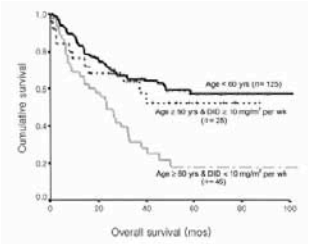
DLBCL: **curable** disease
cf. Elderly advanced NSCLC



Eligibility:
Age 70-
Stage IIIb, IV
PS 0 - 2

Gridelli et al. J Natl Cancer Inst 2003; 95: 362-72.

Anthracycline: the key drug



Korean retro study[1]
125 Pts DLBCL age<60
70 Pts DLBCL age≥60
DXR based therapies

US large data base[2]
9,438 DLBCL age ≥65
Any doxorubicine use:
29% increase CHF risk

[1]*Lee et al. Cancer 2003; 98: 2651-6.*
[2]*Hershman et al. J Clin Oncol 2008; 26: 3159-65.*

高齢者DLBCLにまつわるジレンマ

効果　vs　毒性

⇩

Cure　vs　TRM

“Fit” vs “Unfit”

- “Fit”な患者をいかに選別するか

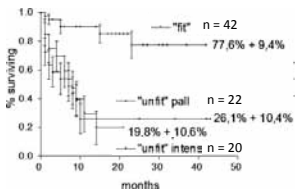
Comprehensive Geriatric Assessment

- 高齢者の総合的機能評価に対して多角的に評価
- 近年多数の高齢者悪性疾患で予後や治療選択で活用

評価項目:
ADL:食事、入浴、トイレ、歩行、階段
IADL:買い物、調理、洗濯、服薬、金銭管理、乗り物の利用
視聴覚、身体機能に影響を与えやすい合併症
認知機能(記憶、見当識、判断力など)
抑うつ度、意欲、QOL
社会性:居住形態、キーパーソ、経済状態、地域社会との交流、介護保険の利用の有無、介護負担度など

Extermann &Hurria J Clin Oncol 2007; 25: 1824-31.

CGAがfit/unfitをより正確に予測する



84 pts DLBCL in
Single institution
Age > 65
"Fit" patients: age<80, low ADL score, less comorbidities

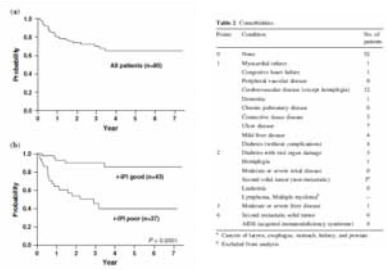
Tucci et al. Cancer 2009; 115: 4547-53.

Charlson Comorbidity Index

- 10年間の観察研究のデータベースを基に各疾患に1～6のポイントを配分
- 頭頸部がん、非小細胞肺がん、膀胱がんなどのにおいてpredictorとしての有用性

Charlson et al. J Chronic Dis 1987; 40: 373-83.

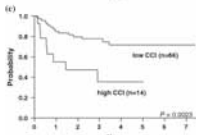
Charlson index for elderly DLBCL



80 pts DLBCL in
Single institution
Age > 65
72 given CHOP±R
14 had CCI≥2

Kobayashi et al. J Cancer Res Clin Oncol 2011; 137: 1079-84.

Commorbidity but not very old age predicts survival for elderly DLBCL



Mean RDI: 0.64 vs 0.47 (p=0.04)
ORR: 93% vs 64% (p=0.02)

Table 3 Univariate and multivariate analysis of risk factors that affected overall survival

Risk factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
ECOG PS ≥ 2	2.84 (1.23–6.50)	0.0154*	2.41 (0.96–5.87)	0.0587
LDH > normal	9.67 (2.83–60.5)	<0.0001*	9.37 (2.36–67.86)	0.0008*
Extranodal sites ≥ 2	3.26 (1.38–7.46)	0.0079*	0.94 (0.34–2.72)	0.9065
Ann Arbor stage III–IV	2.86 (1.25–6.89)	0.0129*	1.00 (0.35–2.80)	0.9926
CCI ≥ 2	3.47 (1.39–8.04)	0.0093*	4.44 (1.63–11.3)	0.0045*
Age > 80	1.33 (0.39–3.54)	0.6166	NA	NA

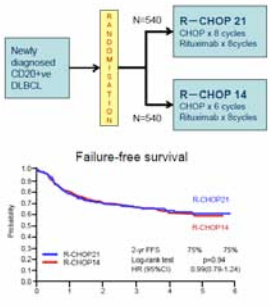
Kobayashi et al. J Cancer Res Clin Oncol 2011; 137: 1079-84.

IPI in Elderly DLBCL

- High-riskにおけるdose intensification
- Low-riskにおけるcombined modality

A Phase III trial comparing R-CHOP14 and R-CHOP21 for the treatment of newly diagnosed diffuse large B cell lymphoma

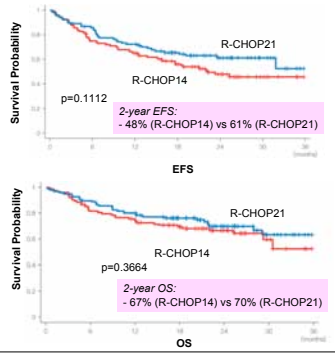
ASCO 2011 Chicago



- In patients receiving rituximab, CHOP14 for 6 cycles is not superior to CHOP21 for 8 cycles
- No obvious sub group appears to derive a greater benefit from R-CHOP14, including age > 60, high IPI, high MIB1 or non-GC phenotype
- As expected a higher frequency of neutropenia was observed in R-CHOP21 which reflects the primary prophylaxis with G-CSF in R-CHOP14

(Cunningham D. et al. ASCO2011 #8000)

R-CHOP-14 vs R-CHOP-21[1]

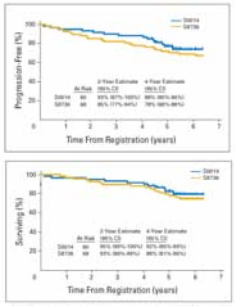


GELA's P3 trial
103 vs 99 DLBCL Pts
Age 60-80
Stage II-IV
ECOG PS 0-2
aaIPI 1-3

"Time to remember to forget Dose-intensification in Lymphoma[2]"

[1] Delarue et al. ASH meeting 2009 #406
[2]Cheson et al. J Clin Oncol 2011 29: 3954-6

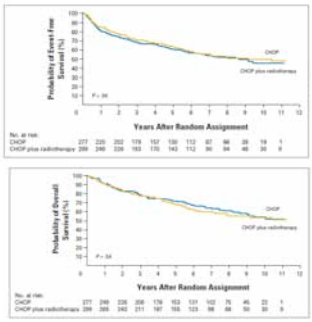
R-CHOP (3) + IFRT



SWOG's P2 trial
60 aggressive B-NHL Pts
70 Pts DLBCL age≥60
Stage I/II
At least 1 risk factor

Persky et al. J Clin Oncol 2008; 26: 2258-63

CHOP (4) vs CHOP (4) + RT (40Gy) in elderly DLBCL



GELA's P3 trial
277 vs 299 aggressive NHL
187 vs 223 DLBCL Pts
age≥60 (median 69 vs 68)
Stage I/II
8 vs 9 % had bulky disease
No risk factor

Bonnet J Clin Oncol 2007; 25: 787-92.

Dose modification

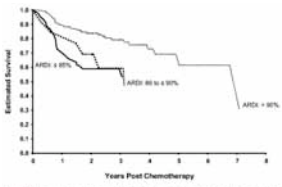
- Significance of RDI in the R-CHOP era
- Dose modified regimen for elderly DLBCL

Relative Dose Index (RDI)

- RDI = $\frac{\text{Actual dose per specific period}}{\text{Planed dose per specific period}}$
- DLBCLにおいては高いほど治癒率が高い

Dixon et al 1986. J Clin Oncol 4:295–305
Kwak et al.1990 J Clin Oncol 8:963–77
Epelbaum et al 1990. Cancer 66:1124–9
Lepage et al 1993. Ann Oncol 4:651–656

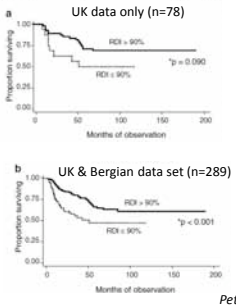
RDI in DLBCL, Pre R era



Belgian retro study
348 pts DLBCL
CHOP-like or others
59% of Pt. Age > 60

Bosly et al 2008. Ann Hematol 87:277–83

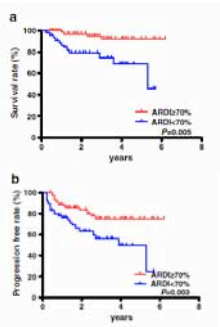
RDI in DLBCL, CHOP-21



UK & Belgian retro study
289 pts DLBCL
CHOP-21 only
Age: NA

Pettengell et al. 2008. Ann Hematol 87:429–30

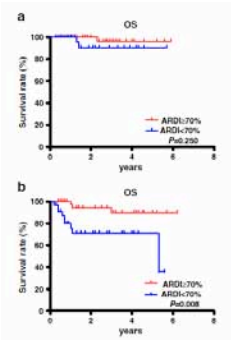
RDI in DLBCL, R-CHOP era



Japanese retro study
152 pts DLBCL
101 Pts treated with R-CHOP
51 Pts treated with R-THPCOP
75% Pts age > 60
49% Pts in H/HI
Age>60, FN & THP associated with lower RDI
Prophylactic G-CSF associated with higher RDI

Hirakawa et al. Ann Hematol 2010; 89: 897-904.

RDI in DLBCL, R-CHOP era

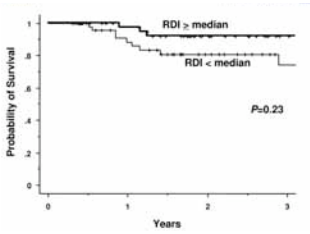


IPI: L/LI (n=77)

IPI: H/HI (n=75)

Hirakawa et al. Ann Hematol 2010; 89: 897-904.

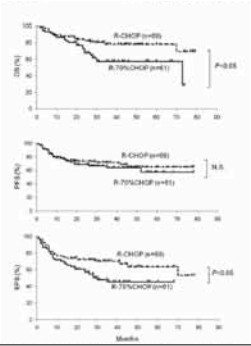
RDI in DLBCL, R era



Japanese retro study
100 Pts treated with R-CHOP
49% Pts age > 60
42% Pts in H/HI
Age>60 associated with lower RDI
RDI trended poor OS [HR per 0.1 of RDI: 0.8 (0.6-1.0) p=0.08)

Terada et al. J Exp Clin Cancer Res 2009; 28: 116.

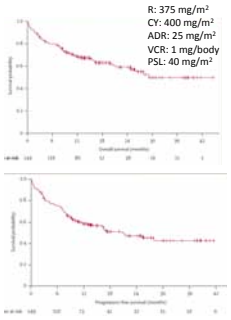
R-70%CHOP



61 pts DLBCL
Single institution, retro
Age > 70
Stage I – IV
Same CR
Severe AEs in elderly

Meguro et al.
Leuk Lymphoma 2012; 53: 43-9.

R-miniCHOP



150 pts DLBCL
Multicenter P2
Age ≥ 80
Stage Ix – IV
PS 0 – 2
OR 73% & CR 62%
AaIPI, hypoalbuminemia, ADL associated with OS

Peyrade et al.
Lancet Oncol 2011; 12: 460-8.

Dose modification for elderly DLBCL

- 許容intensityはhealth statusに依存する
- 至適intensityはdisease statusに依存する

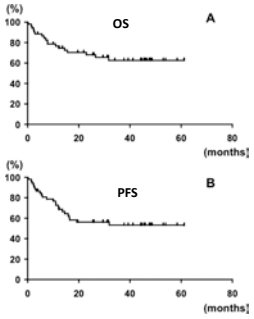
⇒標準化より個別化を図るべき

Miura et al. Lancet Oncol 2011; 12: 725

Alternative regimens

- Alternates for doxorubicine

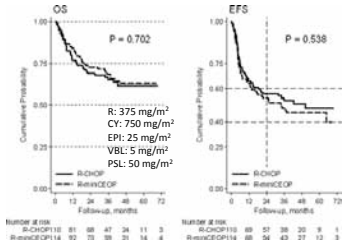
R-THP-COP



52 pts DLBCL
Multicenter P2
Age 70 - 80
Stage II – IV
PS 0 – 3
OR 96% & CR 63%
Poor PS & high LDH correlate with response and OS
P3 vs R-CHOP ongoing

Kasahara et al. Leuk Lymphoma 2011; 52: 629-34.

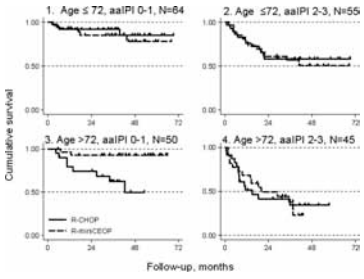
R-CHOP vs R-miniCEOP



110 vs 114 pts DLBCL
Multicenter P3
Age > 65
'Fit' for CGA
Stage II – IV
PS 0 – 3
CR 73 vs 68%

Merli et al. Leuk Lymphoma. Epub ahead of print

R-miniCEOP preferred in elder and low risk patients

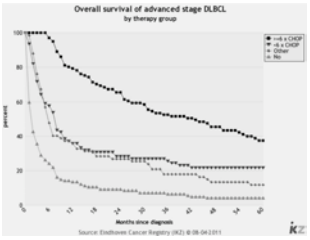


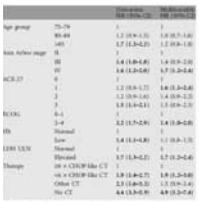
Merli et al. Leuk Lymphoma. Epub ahead of print

Unfitの患者に対して

- Best supportive careがBestか？

Two side of the medallion…





Dutch retro study
419 DLBCL Age≥75

van de Schans et al. Ann Oncol; Epub ahead of print

Relapse/refractory elderly DLBCL

- R-CMD:
  65歳以上30例でCR 57%、2yOS 45%
- 70% R-IVAD:
  70歳以上10例でCR 50%、2yOS 50%

Niitsu et al. Cancer Sci 2006; 97: 933-7.
Miura et al. Int J Hematol; 94: 90-6.

ジレンマに対する現時点での回答

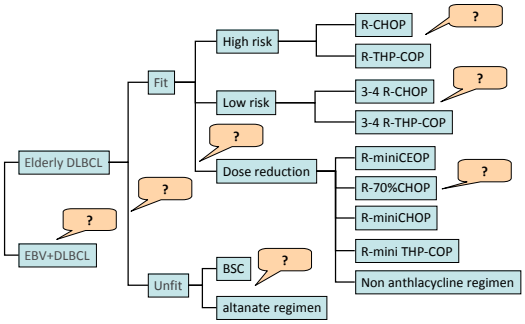
- 高齢DLBCLのもつ背景は多様である
- 単一の戦略を確立することは事実上不可能

⇔R-CHOPを軸に高度に個別化

今後の開発

– 治療強度設定に対する意思決定ツール
– 至適治療強度を算出するアルゴリズム

Future directions



Data mining

- The fourth paradigm of science

- Experimentation, Theory, Computation/Simulation -

Tony Hey. Harvard Business Review Nov. 2010
Bellazzi et al Wiley Advanced Review 2011 1: 416-30

高齢DLBCL患者に対する客観的バイオマーカーに準じた至適治療強度推定モデルの確立（案）

- 目的
  併存疾患スコアや血清総蛋白等のバイオマーカーが化学療法の効果・毒性および予後等の治療アウトカムに与える影響を探索的に解析し、高齢DLBCL患者に対する至適治療強度を推測する意思決定モデルの確立を目指す
- 方法
  調査表記入による多施設協同後方視研究

血清TPはtolerabilityを予測する

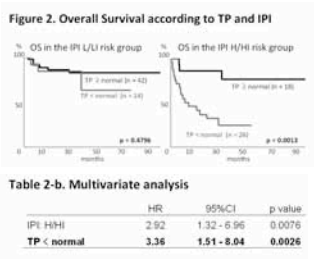


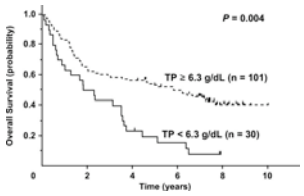
Table 2-b. Multivariate analysis

	HR	95%CI	p value
IPI H/HI	2.92	1.32 - 6.96	0.0076
TP < normal	**3.36**	**1.51 - 8.04**	**0.0026**

100 pts DLBCL in single institution
Various treatment
Age > 65
Stage I – IV
PS 0 – 4

Miura et al. Ann Oncol 2010. 21(suppl 9): 40

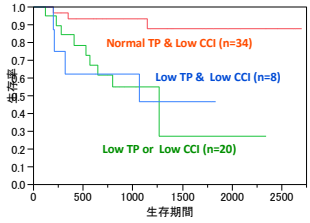
血清TPはPTCLsにおいてprognostic marker となる



131 pts PTCLs in multicenters
Various treatment
Various age

Watanabe et al. Leuk Lymph 2010. 51: 813-21

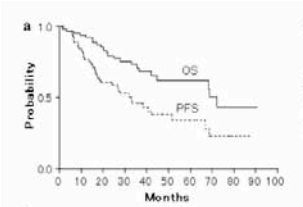
血清TP/CCIは’Fit/Unfit’を予測しうる



62 pts DLBCL
All given R-CHOP
Age > 65
Stage I – IV, PS 0 – 4
Mean RDI 66 vs 54 vs 44%
(p<0.01)

Unpublished

Does more intensive therapy have effects on MCL?

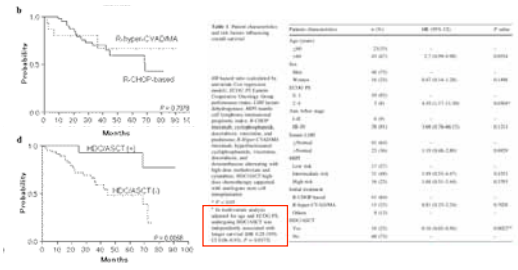


「未治療マントル細胞リンパ腫における化学療法および造血幹細胞移植に対する後方視的多施設共同研究」

64 Pts MCL
Various treatment
Median Age = 64
25% Pts given ASCT

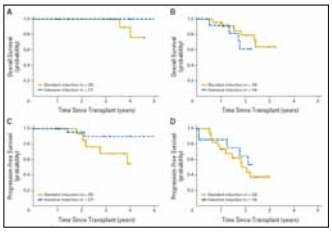
Miura et al. Int J Hematol 2011 93 :684–6

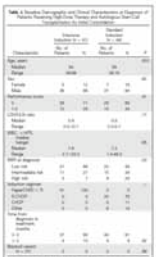
Induction; no.
Consolidation; probably yes.



Miura et al. Int J Hematol 2011 93 :684–6

Induction regimen did not predicts survival for MCL given ASCT





Budde et al. J Clin Oncol 2011: 29; 3023-9