

Improving outcome for patients with Burkitt lymphoma



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DISCLOSURES

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 - Roche, Pfizer, Gilead
 - Honoraria
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 - Advisory board
 - Roche, Celgene
 - Speakers bureau and expert testimony
 - none
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The man behind the name



It is better to read a little and ponder a lot than to read a lot and ponder a little.

Denis Parsons Burkitt

508 THE BRITISH JOURNAL OF SURGERY

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A KARCINOMA INVOLVING THE JAW IN AFRICAN CHILDREN

by DENIS BURKITT

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Maximum tumours of the jaw in children, primary or secondary, are generally regarded as rare. A carcinoma involving the jaw in African children has recently come to be recognized at Stedje Hospital as a distinctive dental condition and certainly the commonest malignancy of childhood.

Twenty-eight patients with this carcinoma in the jaws have been seen during the past 7 years; 21 of

In most cases the tumour started in the region of the alveolar process of a molar (Fig. 1A) or the mandible (Fig. 1B). Loss of the alveolar process was often the first symptom, the teeth in the involved area soon becoming embedded in tumour tissue (Fig. 1C), and losing their position in time. The next stage was irregular displacement of the teeth due to their falling out. The tumour grew rapidly.



FIG. 1A—Dorsal view of carcinoma in alveolus.



FIG. 1B—Carcinoma involving the jaw, resulting in displacement of teeth.

them were seen at Stedje Hospital and four dental hospitals. The tumour was diagnosed clinically in a further 3 children, but these have not been included in this series owing to lack of histological confirmation.

Reports of such a carcinoma of the jaw in African children have been made in the literature (Christensen, 1925; Johnson and Thompson, 1926; Burkitt, Anderson, and Robinson, 1944). Garland (1957) published an illustration of a carcinoma of the jaw in an African child without clinical details.

GEOGRAPHICAL DISTRIBUTION

Tumours have not been limited to the particular area in Uganda, and have appeared in different tribes. The carcinoma has also been observed in Kenya (Clifford, 1950), Tanganyika (Morris, 1951; Burkitt, 1951), Sierra Leone (Thomas, 1951), the Belgian Congo (Felix, 1951), and Southern Rhodesia (Graham, 1957). Tumours with this appearance have not yet been recognized in Johannesburg (1958), 1958; Kharasani (Taylor, 1958); Lusaka (Shah, 1958); or Lourenço Marques (Felix, 1958).

CLINICAL FEATURES

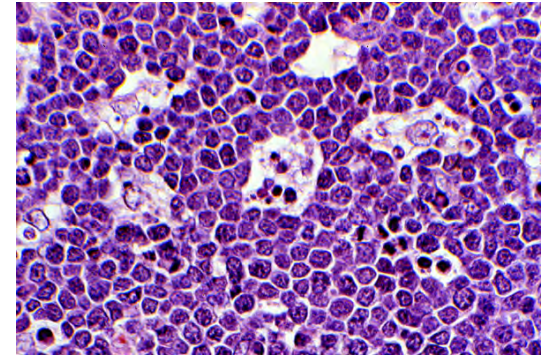
These patients were from 2 to 14 years of age, 20 being between the ages of 1 and 7 (Fig. 1A).

Generally involving the jaw. In only one patient (Case 20) did it extend through the skin. Onset of the tumour and extension of the carcinoma indicated extension of the teeth, and if the patient survived the eye tumour progressed and finally destroyed. Late commonly the tumour presented as a swelling high in the mandible with early invasion of the teeth (Fig. 1A). Pain was not usually an early symptom but would have been expected from the appearance of the tumour. Within two or three months of onset of carcinoma deep ulcers covered the majority of the children from hospital in a moribund condition.

Unless secondary infection occurred, which was not usual, the regional lymph-nodes were not

Burkitt lymphoma

- Rare B-NHL (1-2%), typically affecting children and young adults
- Endemic, sporadic, immunodeficiency-associated
- Monomorphic medium-sized transformed cells with extremely short doubling time
- Immunophenotype: strong mIgM, CD10+, BCL6+, BCL2-, TdT-, Ki67 > 90% (≥99%)
- Cytogenetics: Ig-MYC +, BCL2-, BCL6-
- Frequent extranodal and leukemic presentation
- Genetically relatively stable



Diagnosis and classification

- Elder days
 - ALL – L3;
 - high-grade NHL, small-noncleaved cells
 - New age
 - Burkitt lymphoma / leukemia vs.
 - Burkitt-like NHL (REAL)
 - DLBCL (WHO 2004)
 - B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (aka grey-zone) (WHO 2008)
-

Treatment

Elder days

- ALL – L3

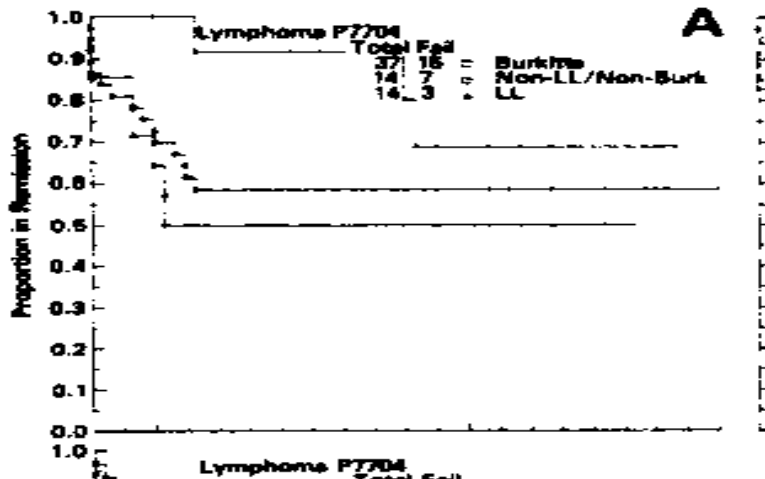
ALL type th

- high-grade NHL, small-noncleaved cells

CHOP-like th

Intermediate phase

HD-MTX based th



Magrath et al, Blood 63:1102, 1984

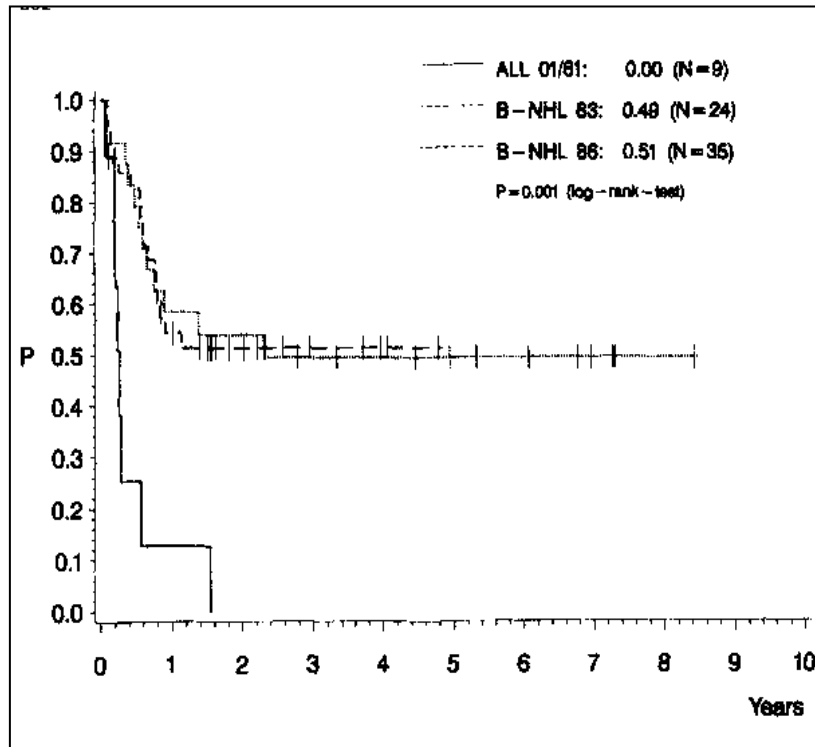
Ramirez et al, Cancer Chemother Pharmacol 3:103, 1979

New age

HD-MTX+R based th

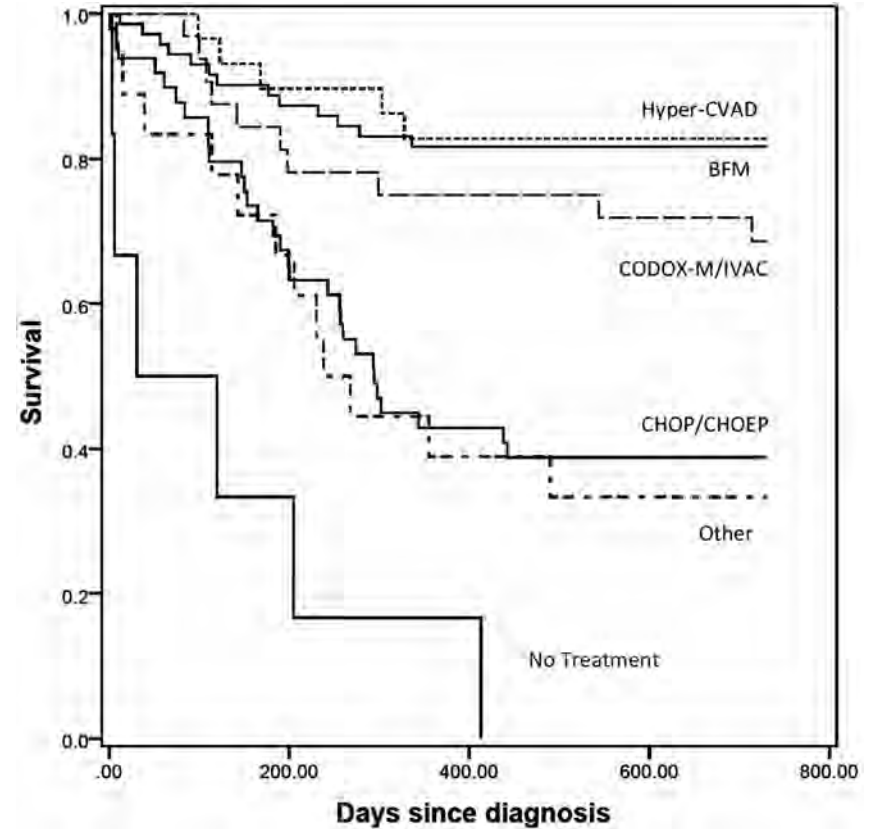
Improvements in results overall survival

Burkitt leukemia



Hoelzer et al. Blood 1996; 87:495

Burkitt lymphoma



Wästerlid et al. Ann Oncol 2013;24:1879-1886

(some pts. also received rituximab)

What about rituximab?

Retrospective comparisons

some find improvement in OS

(reviewed in Wildes et al 2014)

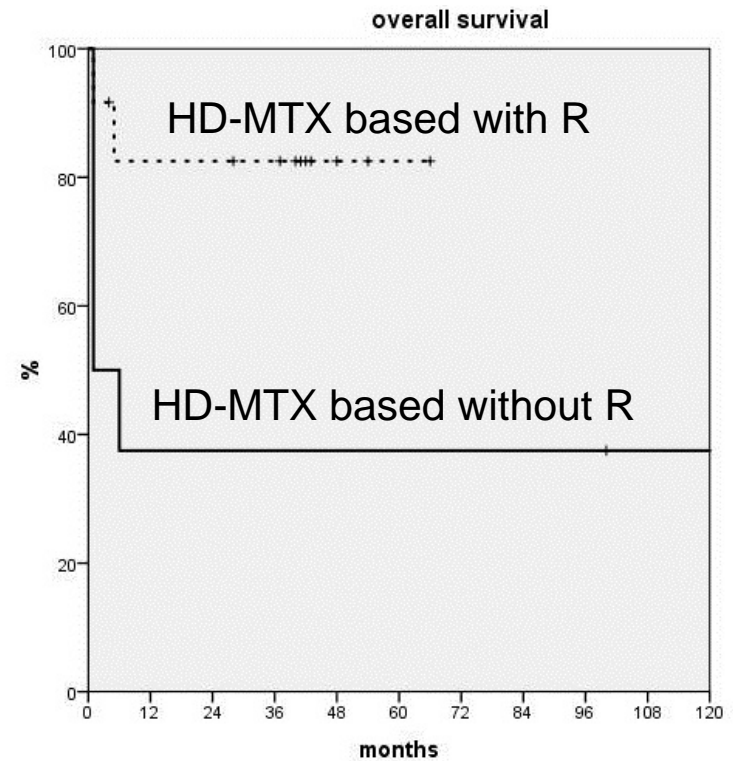
some don't

(Todeschini et al 2012, Wasterlid et al 2011&2013, Kojima et al 2014)

Question uninteresting, toxicity of rituximab negligible, price acceptable, probably useful

therefore

use it!



Dujmović et al, Acta Haematol, 2013

Which HD-MTX based regimen?

Countries of origin

- USA- Stanford, Hyper-CVAD, CALGB
 - UK – CODOX-M/IVAC
 - F – LMB
 - D – B-NHL 86, B-NHL 2002

 - CALGB = B-NHL 86 with increased Ara-C dose
-

HD-MTX based regimens

Dose intensity (mg/m²/3 wks)

	Hyper-CVAD	CODOX-M/ IVAC	B-NHL 86m	CALGB	B-NHL 2002
cyclophosphamide	900	800	500	500	333
ifosfamide	0	3750	2000	2000	1333
MTX	500	1500	1500	1500	1500
Ara-C	6000	4000	300	1000	1533
vincristine*	2	1	2	2	1.67
vindesine*	0	0	0	0	1.67
etoposide	0	0	100	80	167
teniposide	0	0	0	0	67
doxorubicin	25	25	25	25	17

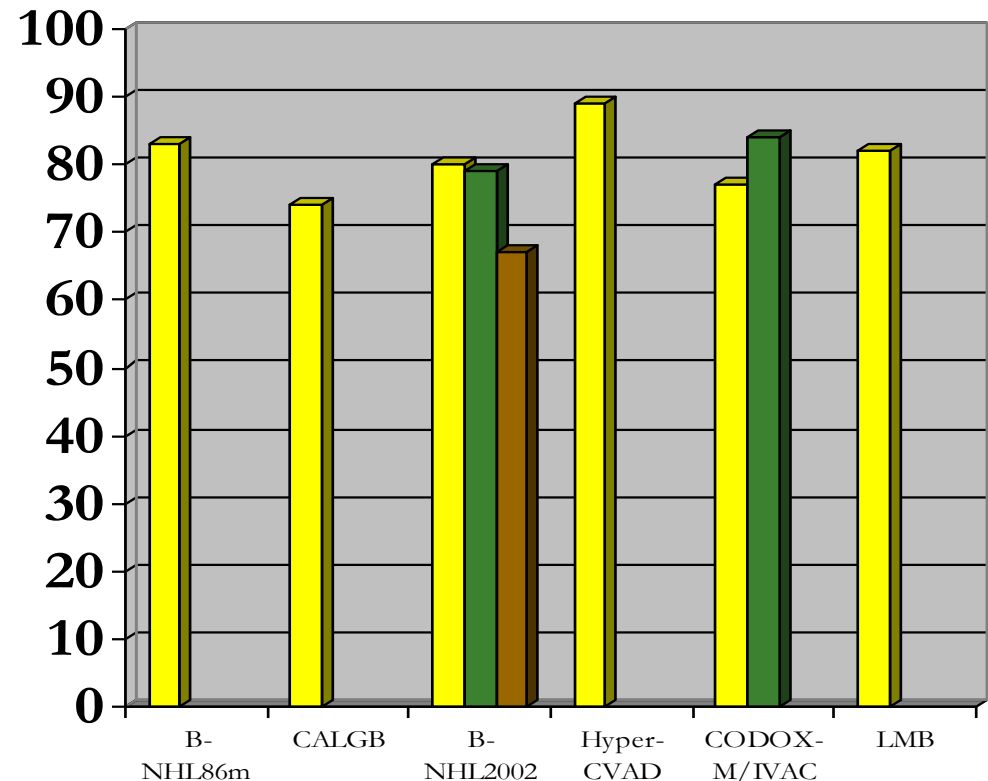
* total dose

R-HD-MTX based regimens

Outcomes

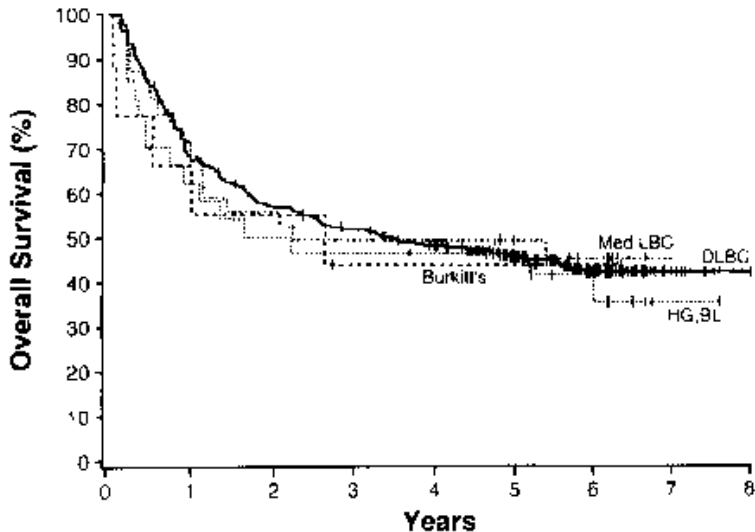
- Modified B-NHL 86
 - 3y OS 83% (Dujmović et al 2012)
- CALGB
 - 4y OS 74% (Rizzieri et al 2014)
- B-NHL 2002
 - 3y OS 80% (Hoelzer et al 2014)
 - 2y OS 79% (Ribera et al 2013)
 - 3y OS 67% (Intermesoli et al 2013)
- Hyper-CVAD
 - 3y OS 89% (Thomas et al 2006)
- CODOX-M/IVAC
 - 2y OS 77% (Barnes et al 2011)
- ibid + liposomal dox & HD-R
 - 2y OS 84% (Evens et al 2013)
- LMB
 - 3y-OS 82% (Ribrag et al 2012)

2-4 y OS (%)



Population-based studies

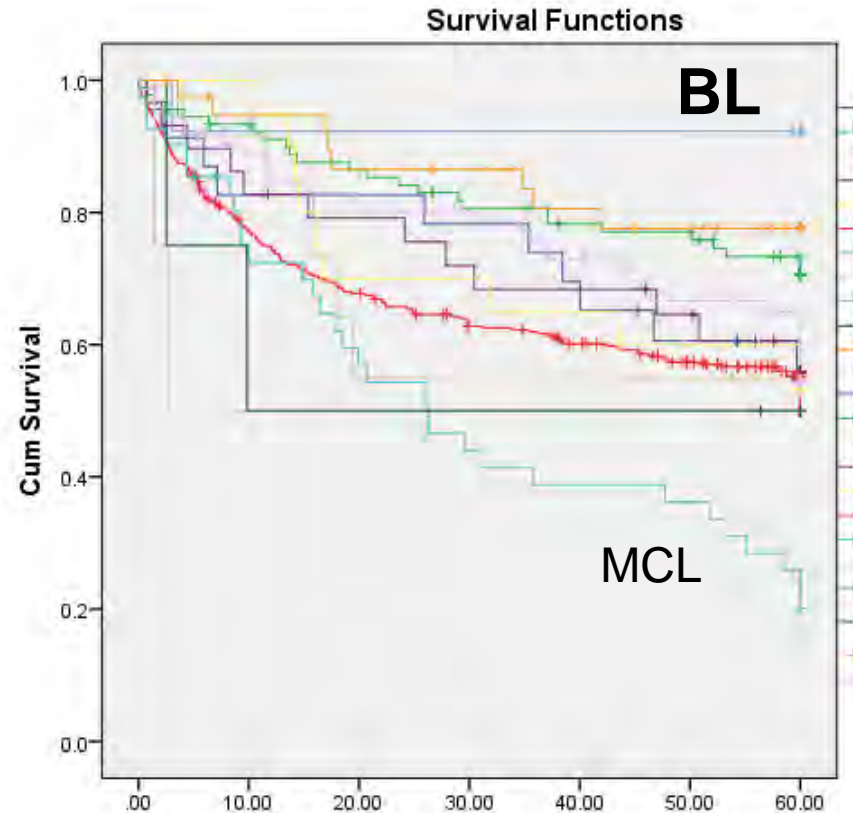
- **Clinical Evaluation of the ILSG: Classification of Non-Hodgkin's Lymphoma By The Non-Hodgkin's Lymphoma Classification Project, Blood 89:3909,1997**



A not-so-bad lymphoma w/o R

Pts. treated 1988-1990

- **KroHem 2015**



The best lymphoma with R

Pts. Treated 2007-2008

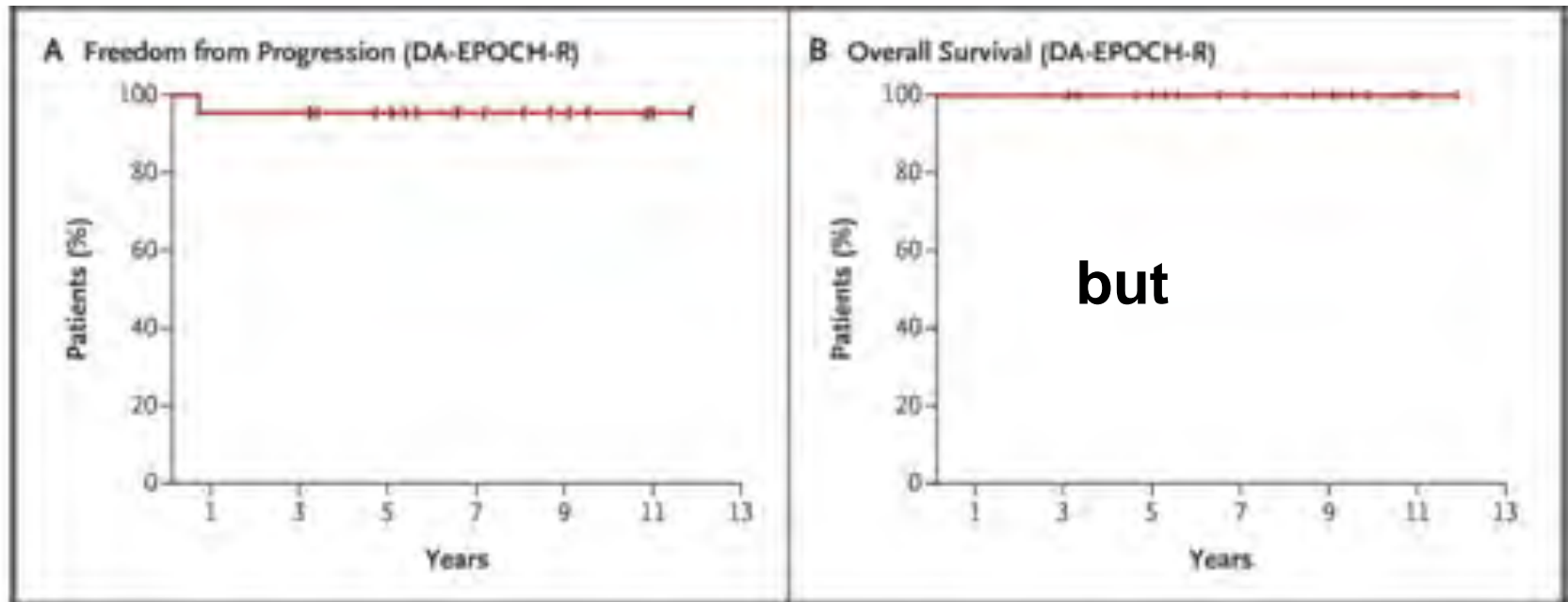
What is the issue in improving outcomes in BL?

- Toxicity of HD-MTX based therapy
 - grade III-IV universal
 - hematological, mucositis
 - TRM up to 20%
 - tumor-lysis related
 - after 1st cycle
 - hematological & infectious
 - during whole treatment
- Efficacy in high-risk populations
 - Elderly & renal failure
 - Toxicity
 - CNS involvement, stage IV, poor PS, IPI, gender
 - HIV+
 - ↑ risk & toxicity
 - HD-MTX+R based regimens feasible and effective

Possible solution

DA-R-EPOCH

- Dunleavy et al. NEJM 369:1915, 2013



- Aurer et al, Ann Hematol 93:177, 2014
- 3 pts. 2y-PFS 0%, 2y-OS 33%

How to solve the dilemma?

- Randomized trial
 - HOVON is doing it
 - EHALyG based registry
 - **In the meantime**
 - Keep doing what you do and wait
 - Diagnose pts. rapidly, watch pts. treated with R-HD-MTX-based therapy carefully and give optimal supportive care
 - Treat elderly, comorbid and pts. with renal failure with DA-R-EPOCH
-

Future I

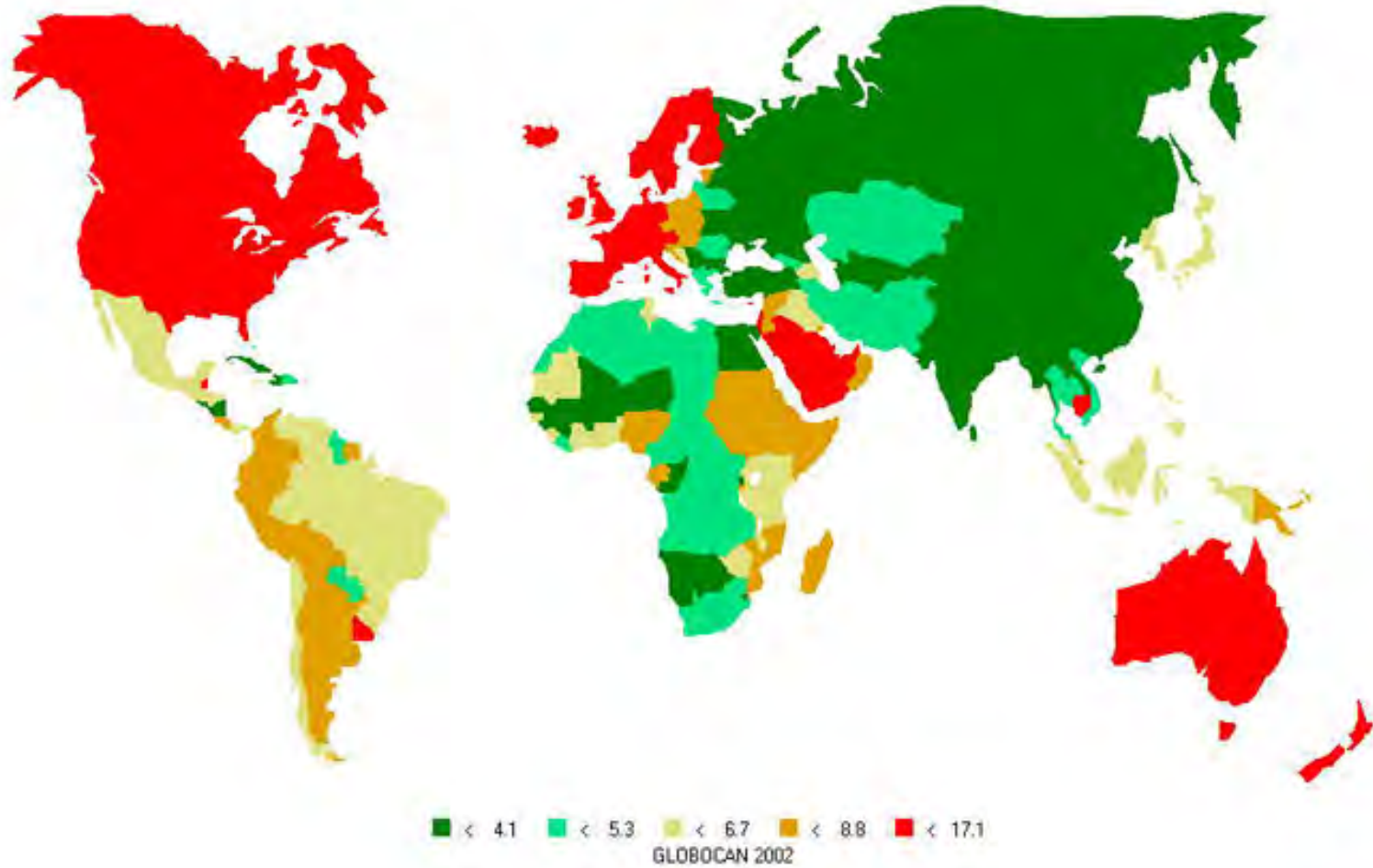
- BL cells strongly dependent on*
 - MYC and TCF3 transcription factors
 - BET bromodomain inhibitors
 - BCR tonic signalling through PI kinase pathway
 - Ibrutinib, idelalisib,...
 - CCND3 - cyclin D3
 - PD-0332991
- One of the targeted agents is going to work
- Easier to combine with DA-R-EPOCH than with R-HD-MTX-based therapies

* Schmitz et al, Nature 490:116,2012 & Cold Spring Harb Perspect Med 2014 4:a014282

Future II

- Quote:
 - These new insights into Burkitt lymphoma pathogenesis suggest new therapeutic strategies, which are sorely needed in developing regions of the world where this cancer is endemic.
 - Because of pricing issues this is probably not going to happen
 - Two standards: similar in efficacy, different in toxicity
 - 1. For the rich and mighty
 - DA-R-EPOCH + targeted agent
 - 2. For the less affluent
 - Anti CD20-HD-MTX-based therapy
-

Incidence of Non-Hodgkin lymphoma: ASR (World)-Male (All ages)





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