ROLE OF RADIOTHERAPY AND DOSE-DENSIFICATION OF R-CHOP IN PRIMARY MEDIASTINAL B-CELL LYMPHOMA: A SUBGROUP ANALYSIS OF THE UNFOLDER TRIAL OF THE GERMAN LYMPHOMA ALLIANCE (GLA)

Author(s): Gerhard Held, Lorenz Thurner, Viola Pöschel, Christian Berdel, German Ott, Christian Schmidt, Andreas Viardot, Walburga Engel-Riedel, Peter Borchmann, Ofer Shpilberg, Mathias Witzens-Harig, Norbert Frickhofen, Maike Nickelsen, Frank Griesinger, Beate Krammer-Steiner, Andreas Neubauer, Massimo Federico, Peter de Nully Brown, Stephan Stilgenbauer, Niels Murawski, Bettina Altmann, Lorenz Truemper, Heinz Schmidberger, Christian Ruebe, Jochen Fleckenstein, Norbert Schmitz, Markus Loeffler, Marita Ziepert

Background

Primary mediastinal B-cell lymphoma (PMBCL) is a distinct entity of aggressive lymphoma, which typically presents in young patients (pts) with a bulky mediastinal mass. Therapy is based on R-CHOP or similar regimens. The role of treatment intensification and consolidative radiotherapy (RT) is controversial, because data from randomized trials are rare.

Aims

In a planned PMBCL-subgroup analysis from the UNFOLDER trial we investigated the role of treatment intensification and RT.

Methods

The UNFOLDER trial included 18-60 year-old pts (aaIPI=0 with Bulk [≥7.5 cm] or aaIPI=1) qualifying for radiotherapy to Bulk or extralymphatic involvement (E). Pts were randomized in a 2 x 2 factorial design to 6xR-CHOP-14 or 6x-R-CHOP-21 without or with RT (39.6 Gy) to Bulk and E. Primary endpoint was event-free survival (EFS), secondary endpoints were progression-free (PFS) and overall survival (OS). Response was evaluated by the Internat Standardized Response Criteria (Cheson 1999).

Results

131 PMBCLs were included with a median age of 34 years, 54% were female, 79% had elevated LDH > UNV and 24% had E. 82 pts were assigned to RT (R-CHOP-21: 43; R-CHOP-14: 39) and 49 to no RT (R-CHOP-21: 27, R-CHOP-14: 22). 96% (79/82) of pts assigned to RT received RT per protocol and 5 pts in the no RT arm received unplanned RT (4 after PR and 1 after CR/CRu). RT related toxicity with grade >=3 was found for nausea (2%), oesophagitis/dysphagia (6%), larynx (2%), skin local (2%) and infection (2%). Responses for pts assigned to RT vs no RT were CR/CRu 94% vs 84%, PR 2% vs 10%, PD 2% vs 4%. With a median observation time of 63 months the pooled 3 year rates were for EFS 88% (95% CI: 82-93), for PFS 93% (95% CI: 89-97) and for OS 97% (95% CI: 94-100). 3-year EFS was superior for pts assigned to RT (94% vs 78%; p=0.007), mostly due to

events caused by initiation of RT (n=5) in the no RT arm. In an as-treated-analysis the difference between the RT and the no RT arm was not significant (p=0.136). Regarding PFS and OS no difference between the RT and the no RT arm was detected (PFS: 95% (95% CI: 90-100) vs 90% (95% CI: 81-98), p=0.253; OS: 98% (95% CI: 94-100) vs 96% (95% CI: 90-100), p=0.636). Dose-densification of R-CHOP-21 by R-CHOP-14 did neither improve EFS, PFS nor OS. Not any event was observed within the patient group with aaIPI 0. Within the group of pts with aaIPI 1 two-fold elevated LDH and E-involvement were significant independent risk factors in a multivariate analysis, ($HR[LDH>2ULN]_{EFS}$=4.5 [95%CI: 1.5-13.4], p=0.006 and $HR[E\ involv]_{EFS}$=3.6 [95%CI: 1.2-11.0], p=0.027; $HR[LDH>2ULN]_{PFS}$=7.9 [1.8-34.8], p=0.007 and $HR[E\ involv]_{PFS}$=3.3 [0.7-14.5], p=0.117). Only 4 pts died (all of them with LDH>2ULN). So far two secondary carcinomas have been observed, both in the R-CHOP-21+RT arm.

Conclusion

To our knowledge, this is the largest series of PMBCLs so far, which have been treated in a prospective, randomized trial in the Rituximab era. The results reveal no differences in outcome between R-CHOP-14 vs R-CHOP-21. Pts assigned to RT had a superior EFS mostly due to a higher PR rate in the no RT arm triggering RT, with no differences in PFS and OS. The results suggest a benefit of RT only for pts, who are responding to R-CHOP with PR according to Internat Standardized Response Criteria (Cheson 1999). Testing RT in PET-positive residual tumors in a randomized trial can solve the question, while RT in PET-negative pts is studied in the ongoing randomized IELSG 37 trial. Our results indicate a very favorable 3-year OS of 96% in PMBCL pts treated with R-CHOP. S*upported by Deutsche Krebshilfe, Amgen and Roche*

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