

What is hot in lymphoma?

Bendamustine plus rituximab vs. CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas

Study Group Indolent Lymphomas from Germany conducted a randomized phase III trial with a total number of 549 patients, randomized to rituximab 375 mg/m² on Day 1 with bendamustine 90 mg/m² on Days 1 and 2 every 28 days (B-R) or RCHOP21 for a maximum of six cycles. The histologies were B-R lymphoma 27%/24%, and mantle cell 18%/19%. A total of 260 patients were randomized to B-R and 253 patients to R-CHOP21. The overall response rates (ORRs) were similar in each arm. The complete remission (CR) rates were superior with B-R 40.1 versus 30.8% ($P=0.0323$). The PFS was longer in patients treated with B-R 54.8 versus 34.8 months ($P=0.0002$), hazard ratio (HR) 0.5765 (95% CI, 0.4292–0.7683). The event-free survival (EFS) was 54 versus 31 months ($P=0.0002$). There was no difference in overall survival (OS). The time to next treatment (TTNT) was not yet reached in the B-R arm and 40.7 months in the CHOP-R21 group ($P=0.0002$). Grade 3 and 4 neutropenia were reported in 10.7% of patients treated with B-R versus 46.5% with R-CHOP21 ($P < 0.0001$). More patients were treated with GCSF in the R-CHOP21 arm with use in 20% of all cycles versus 4% in B-R ($P < 0.0001$). There was less alopecia 15 versus 62%, infectious complications ($P=0.0403$), peripheral neuropathy ($P < 0.0001$), and stomatitis ($P < 0.0001$) with B-R. There were more skin reactions in the B-R arm (42 versus 23) ($P=0.0122$). This study raises a question: Is R-CHOP still the standard of care?

Two cycles of ABVD followed by involved field radiotherapy with 20 Gy is the new standard of care in the treatment of patients with early-stage Hodgkin's lymphoma

Germany Hodgkin Study Group (GHSG) included 1,370 patients, randomized in a multicenter trial from 329 institutions comparing two versus four cycles of ABVD followed by 20 versus 30 Gy involved field radiotherapy. There were more toxicities in the ABVDx4 arm and in the 30 Gy radiation therapy arm. At a median follow-up of 79–91 months, there were no differences in OS in the ABVDx4 arm (97.1%) and ABVDx2 arm (96.6%) or the progression-free survival (93.5 versus 91.2%). There were no significant differences in the radiation therapy arms comparing 30 Gy IFRT with 20 Gy IFRT in OS (97.6 versus 97.5%) or PFS (93.7 versus 93.2%). There were no significant differences in OS, FTFE, or PFS in the four arms establishing limited therapy in Stage I and II Hodgkin Lymphoma in patients with low-risk disease as defined by a mass of less than 7 cm, less than 3 lymph node areas of involvement, absence of a large mediastinal mass, and an ESR that is not elevated. That means we can treat patients with smaller doses of cytotoxic drugs and RT and have less early and probably less late toxicity.

MYC translocations are associated with poor overall survival in DLBCL patients in both chemotherapy and immunochemotherapy

Translocations in the MYC gene are a hallmark of Burkitt's lymphoma, but MYC translocations are also present in 3%–9% of Diffuse Large B-cell Lymphoma (DLBCL). Break-apart FISH strategy for MYC rearrangement was incorporated for this study. A total of 229 patients treated with anthracycline chemotherapy and 92 patients treated with immunochemotherapy (95%

R-CHOP 21) were studied. A total of 141 (62%) of patients in the chemotherapy era and 63 (82%) of patients in the immunochemotherapy era had valid FISH results. Translocations in MYC were identified in 9, BCL2 in 36, and BCL6 in 26. Of the MYC translocations, 5 were MYC alone, 2 MYC and BCL2, and 2 MYC, BCL2, and BCL6. In the chemotherapy era with a median follow-up of 11.3 years, the median survival in the MYC negative patients was 112 months but 19 months in the MYC-positive patients ($P=0.002$). In the immunochemotherapy era patients, the median follow-up was 5 years. The median survival was not reached in the MYC-negative patients but 16 months in the MYC-positive patients ($P=0.08$). The combined MYC-negative patient population was superior to the MYC-positive patients ($P=0.001$). DLBCL patients with MYC translocations have a poor outcome with anthracycline-based chemotherapy and R-CHOP [21–23]. This report is a further confirmation of these observations. The double hit patients, those with MYC and BCL2 or MYC, BCL2, and BCL6 had even worse outcome with no long-term survivors. Novel treatment strategies are required for patients with double hit translocations and should be considered for those with MYC alone translocations. Perhaps an answer would be an aggressive strategy as for Burkitt's?

Evaluation of ofatumumab, a novel human CD20 monoclonal antibody, as single-agent therapy in rituximab-refractory follicular lymphoma

A total of 116 patients refractory to rituximab were treated in an international single-arm trial with 8 weekly infusions (dose 1, 300 mg; doses 2–8, 500 or 1,000 mg). The overall median follow-up was 4.7 months. The ORR in the 1,000 mg dose group was 10%. There was one CR. The median duration of response was 6 months with a median PFS of 6.0 months. The ORR in patients refractory to rituximab monotherapy was 22%.

New anti-CD20 antibodies are in development. Those new antibodies have different activities relative to antibody-dependent cell-mediated cytotoxicity, apoptosis, and other characteristics. This study reports on ofatumumab in rituximab-refractory follicular lymphoma. Ofatumumab targets a unique small-loop epitope on CD20. Further studies randomizing patients to rituximab versus ofatumumab with or without chemotherapy will define the potential role of a more pure monoclonal antibody than rituximab therapy in the immunochemotherapy era.

Vitamin D deficiency is associated with inferior event-free and overall survival in diffuse large B-cell lymphoma

Vitamin D is a naturally occurring steroid hormone with effects on calcium homeostasis, cellular differentiation, proliferation, apoptosis, and angiogenesis. 25-Hydroxyvitamin D [25(OH) vitamin D] is clinically used to measure vitamin D stores, and 1,25-dihydroxyvitamin D [1,25(OH)₂] is considered to be the active metabolite of vitamin D. This study tested the hypothesis that 25(OH) vitamin D levels are associated with prognosis in DLBCL. A total of 370 new patients with a median age of 62 years (range, 19–93) were enrolled into the University of Iowa/Mayo Clinic Lymphoma SPORE project. The median follow-up was 36 months (range, 1–77 months). Forty-four percentage of patients had a mild to moderate deficiency (10–24 ng/mL) and 8% (N 5 29) had a severe deficiency (<10 ng/mL). The highest prevalence of vitamin D deficiency was in patients from the Upper Midwest, poor performance status, and high IPI. 25(OH) vitamin D deficiency was

associated with poor EFS and OS and remained after adjustment for IPI treatment and were similar for the subset of patients treated with R-CHOP. DLBCL patients with deficient 25(OH) vitamin D levels had a 1.5-fold risk of disease progression and a two-fold risk of death compared to patients with 25(OH) vitamin D levels within the optimal range after accounting for other patient factors associated with outcome. The EFS and OS differences were not explained by serum albumin, calcium, or 1,25(OH)₂ levels. 1,25(OH)₂ levels predicted EFS and OS independent of 25(OH) vitamin D levels. These data suggest that vitamin D is unlikely to promote tumor growth. Another study from JCO shows the same for DLBCL and T-cell Lymphoma and promotes an important role of Vitamin D supplementation.

PRIMA study results: rituximab maintenance therapy following rituximab chemotherapy for patients with follicular lymphoma

The study where our Institution took part is PRIMA. The question of the benefit of rituximab maintenance in follicular lymphoma has been evolving. The benefit of giving rituximab maintenance has been shown in previously treated patients, but it had not been established in patients who had received rituximab plus chemotherapy, usually cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or cyclophosphamide, vincristine, and prednisone (CVP). In the PRIMA trial, untreated patients with high-tumor-burden follicular lymphoma (N = 1202) were given 8 cycles of induction immunochemotherapy (rituximab plus CHOP [R-CHOP]: 75%; rituximab plus CVP [R-CVP]: 22%; rituximab plus fludarabine, cyclophosphamide, and mitoxantrone [R-FCM]: 3%). In total, 1018 patients had response (complete response [CR]/unconfirmed CR [CRu]/partial response [PR]) after induction and were randomly assigned to receive either maintenance therapy with rituximab (n = 505; 375 mg/m² every 8 weeks for 2 years) or observation (n = 513). Rituximab maintenance therapy led to a 50% reduction in risk of progression vs observation (stratified hazard ratio [HR]: 0.50; 95% confidence interval [CI]: 0.39-0.64; *P* < .0001). The data from PRIMA clearly show a significant failure-free survival advantage with rituximab maintenance therapy. Maintenance therapy with rituximab also prolonged time to next antilymphoma and chemotherapy treatment by 39% and 40%, respectively. At the end of maintenance, nearly 75% of patients (n = 389) had an objective response (66.8% CR/CRu and 7.2% PR) compared with 55% (47.7% CR/CRu and 7.3% PR) of patients following observation (n = 398). Moreover, fewer patients converted from progressive or stable disease to CR with observation following induction vs rituximab maintenance therapy, 30% vs 45%, respectively. Although rates of toxicity were somewhat higher in the rituximab group, these events were manageable (any event: 52% vs 35% with observation). Most events were low-grade infections (grade ≤ 2), 37% for rituximab vs 22% for observation, and rituximab was well tolerated overall. Although longer follow-up is needed to evaluate overall survival (OS), my conclusion from these data is that rituximab maintenance therapy should be given to untreated patients with follicular lymphoma who are receiving induction with rituximab plus chemotherapy.

Panobinostat for the treatment of patients with relapsed/refractory Hodgkin's lymphoma

Panobinostat is a potent pan-deacetylase inhibitor that has shown promising activity in a phase I study of heavily pretreated patients with relapsed/

refractory Hodgkin's lymphoma. It was well tolerated at doses up to 40 mg given 3 days per week, with thrombocytopenia being the primary dose-limiting toxicity; response rate by computed tomography (CT) was 44%. Panobinostat was further investigated in E2214, a single-arm, open-label, phase II study. The aim of this study was to determine the efficacy of panobinostat in patients with relapsed/refractory Hodgkin's lymphoma following high-dose chemotherapy with ASCT. This was a small trial of 129 patients (median age: 32 years; male patients: 66%) who received oral panobinostat 40 mg 3 times per week in 21-day cycles for at least 2 cycles. Responses were assessed by CT/magnetic resonance imaging every 2 cycles. Interim results showed that the primary endpoint of objective response rate (ORR) was 26%, with 3% of patients achieving a CR; the median duration of response was 7.2 months. The disease control rate was 86%, and the tumor reduction rate was 71%. Reversible thrombocytopenia (grade 3/4: 77.5%) was the most common treatment-related adverse event. Although not curative, panobinostat demonstrates disease activity and reasonable tolerability in this difficult to treat population. Therefore, this was a proof of concept study of a class of drugs conducted in a population for whom there is no standard therapy. Based on these findings, panobinostat may be beneficial in selected patients with disease that is difficult to treat successfully.

Lenalidomide ± rituximab for the treatment of relapsed/refractory DLBCL

This next trial compared the efficacy of lenalidomide with and without the addition of rituximab for the treatment of relapsed/refractory patients with DLBCL. Patients (N = 56; median age: 66 years; DLBCL: 87.5%; DLBCL and follicular lymphoma: 10%; transformed non-Hodgkin's lymphoma: 3.6%) were stratified into 2 groups: those with either germinal center B-cell (GCB)-like disease (n = 25) or non-GCB disease (n = 28; includes activated B cells), according to Hans criteria; 3 patients could not be classified. Among the 53 evaluable patients, 40 patients (77.4%) were treated with lenalidomide monotherapy, 10 patients (18.9%) received lenalidomide plus rituximab, and 3 patients (5.6%) received lenalidomide plus dexamethasone. Among patients treated with lenalidomide alone, a significantly higher overall objective response was reported for patients classified as non-GCB (n = 17) vs GCB (n = 23), 53% (CR: 29.4%; PR: 23.5%) vs 8.7%, respectively, *P* = .006. Median PFS also was significantly longer for non-GCB patients treated with lenalidomide alone, 6.2 months vs 1.7 months for GCB, *P* = .004. Among 10 patients who received lenalidomide plus rituximab, all were classified as non-GCB; 3 patients (30%) had an objective response (CR: 1 patient; PR: 2 patients). Therefore, lenalidomide plus rituximab does demonstrate activity in this setting.

REFERENCES

- 1 ASH abstract book; 2010.
- 2 ASCO abstract book; 2010.
- 3 Engert A, et al. *NEJM*. 2010.
- 4 Drake M, et al. *JCO*. 2010.
- 5 Popović L. *Arch Oncol*. 2009.
- 6 Cheson B. *JCO*. 2010.
- 7 CCO Oncology. Available from: www.clinicaloptions.com

VEGF polymorphisms in early cervical cancer

Angiogenesis is essential for tumor proliferation, invasion, and metastasis (1). In the process of tumor angiogenesis, VEGF plays a pivotal role in endothelial cell survival, mitogenesis, migration, differentiation, vascular permeability, and mobilization of endothelial progenitor cells (2). Several VEGF genetic polymorphisms located in the promoter region (–2578CNA and –460 TNC), 5'-untranslated region (+405GNC), and 3'-untranslated region (+936CNT) could affect VEGF protein production (3). That is, –2578CNA and –460 TNC appear to be associated with higher VEGF expression (3), whereas +405GNC and +936CNT appear to be related to lower expression of VEGF (4,5).

Kim et al. (6) hypothesized that VEGF genetic polymorphisms may affect cancer susceptibility, angiogenesis, and survival in patients with early cervical cancer.

Among 215 healthy subjects and 199 early cervical cancer patients who were treated with surgical resection, Kim et al., specifically investigated four genetic polymorphisms within the VEGF gene (–2578CNA, –460 TNC, +405GNC, and +936CNT). VEGF and CD31 microvessel density (MVD) were measured using tissue microarrays constructed from 117 patients who had available tissue. Their results showed that risk of cervical cancer was decreased in subjects with the VEGF –2578A/A genotype (adjusted OR=0.39, 95% CI 0.16–0.96). Angiogenesis measured by CD31 MVD was significantly decreased in patients with the VEGF +405C/C genotype and VEGF –2578C, –460 T +405C haplotype (recessive model; adjusted OR=0.32, 95% CI 0.11–0.99, equally). Moreover, VEGF +405C/C and VEGF –2578C, –460 T, +405C haplotype were significantly related to shorter disease-free survival (adjusted HR=3.18, 95% CI 1.13–8.94, equally) and overall survival (adjusted HR=8.86, 95% CI 1.40–56.08, equally) by multiple Cox regression analysis. Author's conclusion points out that polymorphisms of VEGF genes may affect cancer susceptibility and survival of early cervical cancer by modulating tumor angiogenesis. Prospective study among homogeneously treated patients is warranted.

REFERENCES

- 1 Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. *Nature*. 2000;407:249–57.
- 2 Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*. 2005;23:1011–27.
- 3 Koukourakis MI, Papazoglou D, Giatromanolaki A, Bougioukas G, Maltezos E, Sivridis E. VEGF gene sequence variation defines VEGF gene expression status and angiogenic activity in non-small cell lung cancer. *Lung Cancer*. 2004;46:293–8.
- 4 Watson CJ, Webb NJ, Bottomley MJ, Brenchley PE. Identification of polymorphisms within the vascular endothelial growth factor (VEGF) gene: correlation with variation in VEGF protein production. *Cytokine*. 2000;12:1232–5.
- 5 Stevens A, Soden J, Brenchley PE, Ralph S, Ray DW. Haplotype analysis of the polymorphic human vascular endothelial growth factor gene promoter. *Cancer Res*. 2003;63:812–6.
- 6 Kim YH, Kim MA, Park IA, Park WY, Kim JW, et al. VEGF polymorphisms in early cervical cancer susceptibility, angiogenesis, and survival. *Gynecol Oncol*. 2010. doi:10.1016/j.ygyno.2010.07.035

Aljoša Mandić

MicroRNA biogenesis is required for Myc-induced B-cell lymphoma development and survival

Many tumor cells express globally reduced levels of microRNAs (miRNA), suggesting that decreased miRNA expression in premalignant cells

contributes to their tumorigenic phenotype. In support of this, Dicer, an RNase III-like enzyme that controls the maturation of miRNA, was recently shown to function as a haploinsufficient tumor suppressor in nonhematopoietic cells. Because the Myc oncoprotein, a critical inducer of B-cell lymphomas, was reported to suppress the expression of multiple miRNAs in lymphoma cells, it was presumed that a deficiency of Dicer and subsequent loss of miRNA maturation would accelerate Myc-induced lymphoma development. We report here that, surprisingly, a haploinsufficiency of Dicer in B cells failed to promote B-cell malignancy or accelerate Myc-induced B-cell lymphomagenesis in mice. Moreover, deletion of Dicer in B cells of CD19-cre⁺/Eμ-myc mice significantly inhibited lymphomagenesis, and all lymphomas that did arise in these mice lacked functional Cre expression and retained at least one functional Dicer allele. Uncharacteristically, the lymphomas that frequently developed in the CD19-cre⁺/Dicer^{fl/fl}/Eμ-myc mice were of very early precursor B-cell origin, a stage of B-cell development prior to Cre expression. Therefore, loss of Dicer function was not advantageous for lymphomagenesis, but rather, Dicer ablation was strongly selected against during Myc-induced B-cell lymphoma development. Moreover, deletion of Dicer in established B-cell lymphomas resulted in apoptosis, revealing that Dicer is required for B-cell lymphoma survival. Thus, Dicer does not function as a haploinsufficient tumor suppressor in B cells and is required for B-cell lymphoma development and survival.

Taken from: Ararte MP, et al. *Cancer Res*. 2010;70(14):6083–92.

New strategies in hepatocellular carcinoma: genomic prognostic markers

Accurate prognosis prediction in oncology is critical. In patients with hepatocellular carcinoma (HCC), unlike most solid tumors, the coexistence of two life-threatening conditions, cancer and cirrhosis, makes prognostic assessments difficult. Despite the usefulness of clinical staging systems for HCC in routine clinical decision making (e.g., Barcelona-Clinic Liver Cancer algorithm), there is still a need to refine and complement outcome predictions. Recent data suggest the ability of gene signatures from the tumor (e.g., EpCAM signature) and adjacent tissue (e.g., poor-survival signature) to predict the outcome in HCC (either recurrence or overall survival), although independent external validation is still required. In addition, novel information is being produced by alternative genomic sources such as microRNA (miRNA; e.g., miR-26a) or epigenomics, areas in which promising preliminary data are thoroughly explored. Prognostic models need to contemplate the impact of liver dysfunction and risk of subsequent *de novo* tumors in a patient's life expectancy. The challenge for the future is to precisely depict genomic predictors (e.g., gene signatures, miRNA, or epigenetic biomarkers) at each stage of the disease and their specific influence to determine patient prognosis.

Taken from: Villanueva A, et al. *Clin Cancer Res*. 2010;16(19):4688–94.

Imatinib upregulates compensatory integrin signaling in a mouse model of gastrointestinal stromal tumor and is more effective when combined with dasatinib

Activating mutations in the Kit receptor tyrosine kinase are associated with gastrointestinal stromal tumor (GIST). Imatinib inhibits Kit and is a

front-line therapy for GIST. However, imatinib most often elicits a partial response or stable disease, and most GIST patients who initially respond to imatinib eventually acquire resistance. Thus, improved treatment strategies for GIST are needed. We investigated the role of Src family kinases (SFK) in tumorigenesis in a mouse model of human GIST. The SFKs Src and Lyn were active in GIST, and surprisingly, imatinib treatment stimulated their phosphorylation/activation. We showed that integrin signaling activates focal adhesion kinase and, consequently, SFKs in GIST and that imatinib enhances integrin signaling, implying a role for the extracellular matrix and integrin signaling in tumor maintenance and imatinib resistance. Dasatinib, an inhibitor of SFKs and Kit, inhibited SFK and focal adhesion kinase activation in GIST but also inhibited Kit and Kit-dependent downstream signaling pathways including phosphoinositide 3-kinase and mitogen-activated protein kinase, but not signal transducer and activator of transcription (STAT) signaling. Whereas dasatinib and imatinib alone both produced a minimal histopathologic response, combination therapy improved their efficacy, leading to increased necrosis in GIST. These results highlight the importance of SFK and STAT signaling in GIST and suggest that the clinical efficacy of imatinib may be limited by the stimulation of integrin signaling.

Taken from: Rossi F, et al. Mol Cancer Res. 2010;8(9):1-13.



Robert G. Edwards

Photo: Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences

The Nobel prize in physiology or medicine 2010

Development of human IN VITRO fertilization to bring a happiness to many couples around the world

Dr. Robert G. Edwards was awarded the Nobel Prize in physiology and medicine in 2010, for his contribution in development of human in vitro fertilization. He was born in 1925, Batley, United Kingdom and his affiliation at the time of the award was the University of Cambridge, Cambridge, the United Kingdom.

The inability to conceive a child is a reproductive defect that afflicts more than 10% of all couples worldwide. During the 1950s, Edwards came to realize the potential of IVF as a treatment for this medical condition. What inspired him to take on this challenge was his research on how hormones control critical ovarian functions in mice, such as oocyte maturation and ovulation. By a brilliant combination of basic and applied medical research, Edwards overcame one technical hurdle after another in his persistence to discover a method that would help to alleviate infertility. He was the first to show that human oocytes could undergo in vitro maturation, as well as fertilization in vitro. He was also the first to show that in vitro fertilized human oocytes could give rise to early stage embryos and blastocysts. All of Edwards' accomplishments came together at 11.47 PM, on July 25 1978 with the birth of Louise Joy Brown, the worlds' first child conceived through IVF. Dr. Robert G. Edwards' research has completely transformed the field of reproductive medicine and today close to 4 million babies have been born thanks to the discovery of human IVF.

*Taken from:
http://static.nobelprize.org/nobel_prizes/medicine/laureates/2010/adv.pdf*

Aljoša Mandić

Report from the 8th BUON congress

The 8th Congress of BUON was held in Sibiu, Romania from 8 to 11 September 2010. As the president of the Congress, Dr. Mircea Dediu said that sharing clinical experience and new ideas, along with searching for answers within various controversial clinical issues is the main goal of all medical meetings. This meeting in Sibiu certainly fulfilled the expectations of attendants, giving them the opportunity to be informed about all current advances in experimental and medical oncology.

All together, 138 abstracts were presented: 27 in the form of educational lectures, 46 in the form of oral presentations and there were 65 poster presentations. More than 300 participants attended the Congress.

Each day of the Congress, two parallel sessions were running. On Thursday, September 9, two educational lectures, seven scientific sessions, and seven sponsored symposia were held. Participants had the opportunity to be updated on current news on genitor-urinary, breast cancer, head and neck tumors, colorectal cancer, innovative techniques in radiation therapy, surgical oncology and germ cell line tumors. Debate on breast cancer, given by Dr. Michael Untch, about adjuvant taxanes for high-risk breast cancer patient, took a lot of attention.

Friday brought us news on supportive and palliative care, therapeutical advances in rare tumors, non-colorectal cancer, mRCC. Special attention was paid to breast cancer, especially HR+/ErbB2+ metastatic BC. A very inspired lecture on better ways to personalize medicine, presented by Dr. Alberto Sobrero raised a very interested discussion. Many participants attended the symposium about the management of advanced renal cell carcinoma. A speech given by Prof. Manuela Schimidinger stood out in this session.

Lung cancer was the main topic on Friday. Also, the attendants had the chance to hear all major news from this year's ASCO meeting, on breast, colorectal, lung and genitor-urinary cancers. The session on basic oncology was the opportunity for experimental oncologists to keep up with new findings. One of the most visited lectures that day was a speech given by Dr. Johan Vastenijste about inhibitors of epidermal growth factor receptor.

During the Congress, attendants could visit poster sessions and talk to the authors about their work. That was especially important for young oncologists, giving them the opportunity to share their results and experience.

The social life was very interesting too. Sibiu was the European Capital of Culture in 2007. Sibiu was firstly mentioned in the 12th century, and was originally a Saxon town. Successive rings of fortifications incorporated the Upper Town and Lower Town around a nucleus, comprising Large Square, Small Square and Huet Square, interconnected by streets and arched passageways. It was delightful to walk around, taking a step back in history. From scientific, as well as cultural point of view, we were all extremely pleased to be guests in Sibiu.

Radmila Janković