European patients, and in subgroup analysis of prospective randomized studies. There are few data about the impact of this treatment on QoL.

From April 2010 to April 2011 we prospectively evaluated skin-toxicity related QoL in 15 consecutive pts aged >70 yrs treated with cetuximab for MCRC in our outpatient clinic. After one month of cetuximab therapy skin toxicity was recorded using the CTC NCI 3.0 version and QoL was evaluated using the Dermatology Life Quality Index (DLQI) Italian version. Relationship between cumulative skin toxicity scoring and QoL impact was evaluated with linear regression testing and Anova testing.

Mean age was 74.5 yrs ± 4.5. Two were female pts and 13 male. No patients had previous history of skin illness. Rash and desquamation were detected in all pts (9 G1 and 6 G2), xerosis in 13 pts (12 G1 and 1 G2), nail changes in 5 pts (all G1), hitching in 7 pts (all G1). No skin toxicity >G2 was recorded. Global toxicity score was obtained adding single item scores. DLQI global score showed a small effect of skin toxicity on QoL in 9 pts, a moderate effect in 6 pts and a large effect in no patient. The most affected headings were 'symptoms and feelings' and 'daily activities'. Less important was the impact on 'leisure' and 'personal relationships' and 'work and study'. No relationship was found between toxicity scoring and DLQI scoring.

Skin toxicity after one month of cetuximab therapy in this elderly group of pts was similar to that previously reported in no age-selected population. The lack of severe toxicity may be due to the short duration of therapy when data were recorded and also to the use of prophylactic treatment with UV-filters and skin-moisturizers. DLQI is probably less effective for QoL evaluation in elderly people because it emphasizes some life aspects (work and social relationships) less important in this group than in younger people. Despite this, our data seem to confirm not only the good toxicity profile of cetuximab in elderly people but also its tolerable impact on QoL.

## E35 BRAIN METASTASES (BM) FROM COLORECTAL CANCER (CRC): A SINGLE INSTITUTION EXPERIENCE

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**Background.** BM from CRC are rare (2-4%) and median survival (MS) is dismal (3 months), mainly due to late diagnosis, extensive systemic disease, treatment refractoriness, cerebellar involvement and poor performance status. Although brain imaging is not routinely performed in metastatic CRC, better patients (pts) survival will likely result in increased BM incidence.

**Patients and methods.** A retrospective analysis was performed on CRC pts with BM treated at a single Institution, in order to collect data about clinical features and outcome. Radiation Therapy Oncology Group recursive partitioning analysis (RPA) was used to assess prognosis.

**Results.** From January 2005 to April 2011, 26 consecutive CRC pts with BM were treated at the National Cancer Institute of Milan. All were diagnosed for neurologic symptoms. Median age 60 years (range 41-85), M/F:12/14, 13 (50%) solitary BM, 12 (46%) supratentorial, 7 (27%) cerebellar and 7 (27%) both, mean diameter 27 mm. Twenty (77%) pts had progressive pulmonary disease, 10 (38%) mediastinal involvement, 19 (73%) multiple metastatic sites and only 4 (15%) isolated brain progression. Median time from primary diagnosis and from thoracic metastases to BM was 3 years and 27 months, respectively. Six patients (23%) were treated with surgery and adjuvant/salvage radiation: all had single BM, with younger age and controlled/absent extracranial disease; twenty (77%) pts received radiotherapy alone, either stereotactic, whole brain or both. MS for the overall population was 16.5 weeks; 6-month survival, 34%. MS according to treatment: surgery plus adjuvant/salvage radiotherapy: 12.5 months; radiotherapy alone: 6 weeks. MS according to RPA: class I, 52 weeks; class II, 28 weeks; class III 2 weeks.

**Conclusions.** Diagnosis of BM from CRC is often late and prognosis is extremely poor. RPA III pts should be treated with supportive care alone, while selected RPA I pts can benefit from multimodality treatments. Brain imaging in plurimetastatic CRC pts should be done starting 2 years after initial diagnosis of lung metastases and in case of progressive thoracic disease.

## E36 SPHINGOSINE KINASE 1 (SPHK1) CONTRIBUTES TO RESISTANCE TO EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS IN COLORECTAL CANCER MODELS

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**Background.** Although EGFR targeted agents represent an effective strategy in the treatment of several cancer types, including colorectal cancer (CRC), the clinical use of these agents is significantly limited by intrinsic or acquired resistance. Alterations in the 'sphingolipid rheostat', or the balance between the proapoptotic molecule ceramide and the mitogenic factor sphingosine-1-phosphate (S1P), due to overactivation of sphingosine kinase 1 (SphK1), have been involved in the regulation of resistance to both chemotherapeutics and targeted agents.

**Experimental plan.** Since some studies have described cross-talks between SphK1 and EGFR-dependent signalling pathways, we investigated the involvement of SphK1 in resistance to EGFR inhibitors in CRC models.

**Results.** We used CRC cell models with both intrinsic or acquired resistance to the anti-EGFR monoclonal antibody cetuximab. We found that SphK1 is overexpressed in CRC cells resistant to EGFR inhibitors. Consistently with this data, higher doses of N, N-dimethylsphingosine (DMS), a potent competitive inhibitor of SphK1, are needed to achieve complete enzyme saturation and survival inhibition in resistant cells. Moreover, ceramide induces apoptosis less efficiently in resistant than in sensitive cells, consistently with the idea that increased SphK1 levels mediate S1P synthesis by ceramide in resistant cells. The contribution of SphK1 to the resistant phenotype was supported by the demonstration that SphK1 inhibition by DMS or silencing via siRNA in resistant cells restores sensitivity to anti-EGFR drugs, whereas exogenous SphK1 overexpression in wild-type cells confers resistance to these agents. Finally, treatment of resistant CRC cells with fingolimod (FTY720), a S1P receptor inhibitor,

resulted in re-sensitization to cetuximab even in presence of KRAS mutation. We are now investigating the correlation between SphK1 expression in tissue samples derived from CRC patients with KRAS mutations and response to cetuximab.

**Conclusions.** Our data could contribute to clarify the role of SphK1 in the onset of resistance to EGFR inhibitors and they may suggest SphK1 inhibition as a part of novel targeting strategies potentially effective also in resistant cancer patients.

## E37 TOLERABILITY AND QUALITY OF LIFE IN ELDERLY PATIENTS TREATED WITH BEVACIZUMAB FOR METASTATIC COLORECTAL CANCER

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**Introduction.** The use of bevacizumab, anti-VEGF monoclonal antibody, in combination with regimens based on 5FU/LV (or capecitabine) ± irinotecan or oxaliplatin, considerably improved prognosis of patients with metastatic colorectal cancer (mCRC). However, potential adverse events such as hypertension, proteinuria, bleeding, gastrointestinal perforation and thrombosis should be considered especially in elderly patients. Aim of our study was to assess bevacizumab-related adverse events and their influence on quality of life in two groups of patients with mCRC.

**Patients and methods.** From January 2008 to June 2010 we studied 59 patients with mCRC, receiving first-line chemotherapy plus bevacizumab (5 mg/kg every 2 weeks), divided in two groups, the first of 28 patients aged ≤70 years (range 35-70; mean 58.4 years) and the second of 31 patients >70 years (range 71-79; mean 72.7 years). Patients with impaired renal function and/or proteinuria ≥0.5 g/day were excluded. Adverse events were defined according to the National Cancer Institute Common Terminology Criteria (NCI-CTCAE v3.0.) Quality of life was assessed with FACT-C, EORTC-C30 and CR38 questionnaires. Patients were evaluated at baseline, at each cycle of therapy, three and six months after the end of chemotherapy.

**Results.** Any grade hypertension occurred in 7 (25%) patients ≤70 years and in 9 (29%) older patients. Grade 3 hypertension, requiring the initiation or a change of antihypertensive therapy, was observed in 3 (10.7%) patients ≤70 years and in 4 (12.9%) patients >70 years. Proteinuria occurred in 8 (28.6%) patients ≤70 years and in 9 (29%) older patients. Grade 4 hypertension (hypertensive crisis) and/or grade 4 proteinuria (nephrotic syndrome) was not seen. The FACT-C and EORTC questionnaires showed that bevacizumab-related side effects had no impact on quality of life.

**Conclusion.** In our study combination therapy with bevacizumab was well tolerated with a generally manageable safety profile in all patients. Bevacizumab-related adverse events such as hypertension and proteinuria, while noting more prevalent in patients aged >70 years, had no significant effects on quality of life.

## E38 SAFETY OF BEVACIZUMAB PLUS CHEMOTHERAPY IN METASTATIC CANCER PATIENTS: AN EXPERIENCE IN UNSELECTED POPULATION

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**Background.** Bevacizumab, a humanized monoclonal antibody inhibiting VEGF tumour angiogenetic activity, was approved, in combination with chemotherapy, for treating many types of advanced cancer. Because of the important role of VEGF in vascular function and physiological angiogenesis its inhibition by bevacizumab has been noted to cause serious adverse events, including bleeding, thromboembolic events, bowel perforation and neutropenia.

The aim of this observational retrospective study was to evaluate the safety and the toxicity profile of bevacizumab in addition to several chemotherapeutic regimens in advanced cancer.

**Materials and methods.** From January 2006 to April 2011, 89 patients with metastatic cancer (84 colorectal, 3 renal, 1 breast, 1 lung) were treated with bevacizumab, in addition to different chemotherapeutic regimens (74 patients CPT11+5FUic, 6 FOLFOX4, 4 degramont, 1 paclitaxel, 1 carboplatin-paclitaxel, 3 interferon) in Medical Oncology Department of Azienda Ospedaliera di Desio e Vimercate. Eighty-five (96%) patients received bevacizumab as first-line chemotherapy and 4 (4%) as second-line. The G3-G4 toxicities were recorded according to WHO classification system. Results are based on descriptive analysis of the first toxicity event.

**Results.** Overall G3 and G4 toxicities were reported in 24 patients (27%). Adverse events leading to treatment discontinuation were recorded in 7 patients (7.8%). One death occurred, due to a thromboembolic event (1.1% fatal event).

| Type of ADR | No. G3-G4 ADR (%) | Treatment discontinuation (%) |
|---|---|---|
| Hypertension | 13 (14.60%) | 1 (1.1%) |
| Bleeding | 3 (3.40%) | 1 (1.1%) |
| Thromboembolic events | 2 (2.20%) | 3 (3.4%) |
| Other events | GI disorders 3 (3.4%)<br>Myelotoxicities 2 (2.2%)<br>Cardiac disorders 1 (1.1%) | 2 (2.2%) |

**Conclusions.** According to our experience, bevacizumab plus chemotherapy seems to be a well tolerated treatment in clinical practice, and its safety profile in addition to chemotherapy appears consistent with those reported by other experiences. Hypertension, the most common adverse event, was well manageable and leaded to treatment discontinuation only in one case. Data suggest particular attention to thromboembolic events, being the most frequent cause of treatment discontinuation.

## E39 VALUE OF VIDEOLAPAROSCOPY FOR SELECTION OF PATIENTS WITH PERITONEAL CARCINOMATOSIS FROM COLORECTAL CARCINOMA BEFORE CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

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