

Abstract

Background: Clinical trials may have a selection bias caused by an underrepresentation of pts older than 65 years (y) and of ECOG performance status > 1. Noninterventional studies (NIS) are a helpful tool to evaluate approved therapies in daily practice in the general patient population. The aim of this subgroup analysis of this German NIS was to evaluate the efficacy and safety profile of cetuximab in combination with chemotherapy in irinotecan pretreated mCRC patients aged < 65 and > 65 years.

Methods: Between 04/2005 and 11/2007 the data of 497 irinotecan-pretreated pts with mCRC (out of 657 pts documented) were entered in the database of this NIS. We analyzed both patient groups applying descriptive statistics and χ^2 - or Fishers exact test.

Results: Median age was 66 y [30-88] with 247 and 250 pts of age < 65 and age > 65, respectively. 17.4% and 21.6% of pts in both groups showed an ECOG-Status of 2-3. Pts had 1-4 lines of previous chemotherapy: 26% and 17% 1 line, 43% and 43% 2 lines, 19% and 25% 3 lines, and 13% and 15% 4 lines (p=0.55). Cetuximab was mainly combined with irinotecan in a weekly regimen (71% and 73%) and also combined with 5-FU in 20% and 19% of pts, respectively. Severe cetuximab-related toxicity occurred in 2% (6 and 4 pts, respectively). The median duration of any grade of skin reaction (35 d) was in pts age < 65 significant longer (42 d), than in patients age > 65 (31 d); (p=0.04). However, there was a trend towards higher grade (≥ 2) skin toxicity in pts age > 65. Skin toxicity led to discontinuation of therapy in 2.6% (6 pts in both groups), but in 22% and 31% to a dose modification and in 6% and 11% to a treatment pause. The objective response rates were similar for both groups: 38.1% for age < 65 vs. 36.4% for age > 65 (p=0.57). The rates for secondary resectability of metastases after cetuximab-based therapy were 4.4% for both groups. Time to tumor progression was similar for both age groups: 4 months [range: 1.0-19.0] and 5 months [1.0-17.0] (p=0.79).

Conclusions: Cetuximab has a similar efficacy and safety profile for patients age >65 and \leq 65 years. Therefore these results add valuable information to the clinical trials.

Documentation period: 04\2005 - 11\2007

- 657 patients were documented in the online-documentation database for an individual maximum of 12 months (Aloebis GmbH, Gießen, Germany)
- 497 of the patients were irinotecan pretreated and documentations were completed and signed
- 87 oncology centers participated

Patient Characteristics

	Evaluated Patients (n = 497)	18-65 J. (n = 247)	> 65 J. (n = 250)
Age (range)	66 (30-88)	59	70
18-65 Years	49.7% (n=247)	30-65	66-88
>65 Years	50.3% (n=250)		

Gender %	18-65 J. (n = 247)	> 65 J. (n = 250)
m	64	62
w	36	38

ECOG PS, %	18-65 J. (n = 247)	> 65 J. (n = 250)
0	18	18
1	60	58
2	19	21
3	1	1

Localisation of primary tumor	18-65 J. (n = 247)	> 65 J. (n = 250)
Colon	58	60
Rectum	42	40

Prior Therapy, %	18-65 J. (n = 247)	> 65 J. (n = 250)
Resection of primary Tumor	95	96
Resection of Metastasis or Recurrence	31	34
Radiation	24	28*
Adjuvant Chemotherapy	44	43
Palliative Chemotherapy	100	100

Number of prior Chemotherapies, %	18-65 J. (n = 247)	> 65 J. (n = 250)
0	21	17
1	43	43
2	22	25
3	13	15
4	14	

*p=0.06

	evaluated patients (n = 497)	18-65 Y (n = 247)	> 65 Y (n = 250)
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Combination therapy, %	18-65 Y (n = 247)	> 65 Y (n = 250)
Irinotecan	100	100
5-FU/FA	20	20
Capecitabine	<1	<1

Irinotecan combination therapy	evaluated patients (n = 497)	18-65 Y (n = 249)	> 65 Y (n = 250)
Irinotecan-Dosis, %			
80 mg/m ²	36	38	35
120 mg/m ²	26	26	26
180 mg/m ²	6	7	4
350 mg/m ²	5	4	6
Other Dosis	27	24	30

Application, %	18-65 Y (n = 247)	> 65 Y (n = 250)
Weekly	72	71
Every 2-Weeks	12	13
Every 3-Weeks	8	8
Other	8	8

Non-skin toxicities (NCI)

	18-65 Y (n=247)	> 65 Y (n=250)
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All Grade (1-4) Toxicities, %

	18-65 Y (n=247)	> 65 Y (n=250)
Patients with all grade toxicities	60	55
Gastrointestinal	39	38
Blood/Bone Marrow	22	21
Constitutional Symptoms	15	13
Hepatic	10	10
Pulmonary	7	5
Infection / Febrile Neutropenia	5	4
Renal / Genitourinary	4	4
Hypersensitivity / Immunology	4	4
Patients with severe cetuximab-related adverse events	2% (n=6)	2% (n=4)
1 life-threatening		
8 recovered until end of study		

Grade of toxicities (CTC V2.0), %

	18-65 Y (n=247)	> 65 Y (n=250)
1	41	46
2	39	34
3	14	16
4	3	3

Skin reactions (NCI)

	18-65 Y (n = 247)	> 65 Y (n = 250)
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Skin reactions \geq grade 1

	18-65 Y (n = 247)	> 65 Y (n = 250)
Median duration of skin reactions	42*days	31 days
Dermatologist consulted, %	12	11

Grade (CTC V2.0), %

	18-65 Y (n = 247)	> 65 Y (n = 250)
n.e.	10	6
1	45	39
2	35	40*
3	9	11*
4	0	3

*p<0.05 (post-hoc grade 2-4)

Therapy, %

	18-65 Y (n = 247)	> 65 Y (n = 250)
topical	55	54
systemic	16	14
unknown	30	30

Response to therapy, %

	18-65 Y (n = 247)	> 65 Y (n = 250)
Topical therapy: complete / considerable	56	66
minor / no change	33	27
worse	3	0
Systemic therapy: complete / considerable	67	54
minor / no change	24	28
worse	2	7

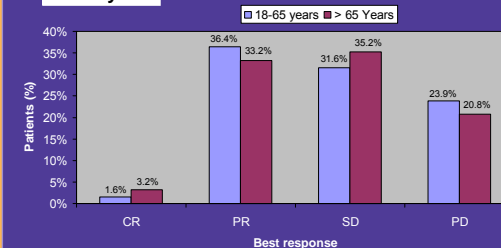
Compliance to cetuximab

	evaluated patients (n=497)	18-65 J. (n = 247)	> 65 J. (n = 250)
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Treatment Time months	18-65 J. (n = 247)	> 65 J. (n = 250)
Median number of cetuximab infusions	15	16 (2-48)
Dose modifications, n	81	45
Treatment pause, n	546	285

Discontinuation of treatment within 12 months observation period, n	18-65 J. (n = 247)	> 65 J. (n = 250)
Reasons, %:		
Progression of disease	62	64
Patient request	11	10
Death	7	7
Adverse event	4	2
Skin reaction	3	3
Severe adverse event	1	1
Lost of contact	1	1
Other	11	12

Efficacy:



	18-65 J. (n = 247)	> 65 J. (n = 250)
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Best response according to prior line of Chemotherapy, %

	CR + PR	CR + PR
1 (n=108)	47	43
2 (n=213)	33	38
3 (n=109)	41	27
4 (n=60)	31	40

Time to Progression (TTP)	18-65 J. (n = 247)	> 65 J. (n = 250)
	4.0 (1-19)	5.0 (1-17)

Objective Response Rate %	18-65 J. (n = 247)	> 65 J. (n = 250)
	38	36

Clinical Benefit (CR + PR + SD)	18-65 J. (n = 247)	> 65 J. (n = 250)
	70	72

Secondary Resectability	18-65 J. (n = 247)	> 65 J. (n = 250)
	4.5% (n=11)	4.4% (n=11)

Conclusions:

- 50% of the patients were > 65 years with a median of 70 years, 22% had ECOG performance score > 1. Patients \leq 65 had similar characteristics and an age median of 59 years, 17% ECOG PS > 1. However, patients \leq 65 years of age were more frequently pretreated with radiation, whereas patients > 65 showed a trend to more lines of chemotherapy prior to combination therapy with cetuximab.
- Patients > 65 showed more skin reactions grade 2-4. However they suffered a significantly shorter duration of skin toxicity compared to the younger patients.
- Topical or systemic treatment of skin reactions resulted in complete or considerable response in the majority of patients.
- No difference of non-skin toxicities were seen between patients \leq 65 and > 65 years.
- There was no difference in efficacy endpoints: Objective Response Rate 38% and 36%, Clinical Benefit 70% and 72%, and Secondary Resectability 4.5% and 4.4% for patients \leq 65 and > 65 years, respectively.
- Cetuximab has a similar efficacy and safety profile for patients age > 65 and \leq 65 years. Therefore these results add valuable information to the clinical trials.