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ORIGINAL PAPER

Metastatic esophagogastric adenocarcinoma: trends in first-line treatment and predictive factors for the implementation of HER2 testing in clinical practice during the first year after trastuzumab market approval

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Abstract
Purpose Little is known about the use of first-line chemotherapy in clinical practice in patients with advanced esophagogastric adenocarcinoma, and no data have been published regarding potential obstacles for the implementation of molecular testing for targeted agents in this patient group. Here, we sought to evaluate factors influencing treatment decisions with special focus on the implementation of HER2 testing during the first year after trastuzumab market approval in Germany.
Methods A total of 754 patients undergoing treatment decisions for palliative first-line therapy in 2010 were documented using Therapiemonitor®. Drug use and intensity of first-line treatment were analyzed. Data on HER2 testing and test algorithm are described, and variables influencing HER2 testing were selected using bivariate analysis. Significant factors were included in a multivariate logistic regression analysis.
Results Compared with previous years, treatment intensity has further increased. The use of chemotherapy triplets rose from 10.1 % in 2006 to 60.3 % in 2010. In 2010, 49.1 % of patients were tested for HER2 and in 52.2 % of these patients the currently proposed test algorithm was used. Using multivariate logistic regression analysis age $\geq$67 years and "initiating institution: practice" were found to negatively impact the likelihood of HER2 testing, while treatment goal "prevention of progression", multiple metastases and a Karnofsky status >80 % showed positive correlation with HER2 testing.

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Conclusion The tendency to use more intensive first-line chemotherapy regimens in patients with advanced esophagogastric adenocarcinoma continued in 2010. Only a minority of patients had an access to the appropriate molecular diagnostics and therefore to treatment with trastuzumab. The access was limited due to the preselection following individual, clinical and institutional factors.

Keywords Chemotherapy · HER2 · Metastatic gastric cancer · Trastuzumab

Introduction

Gastric cancer is the second most common cause of cancer death worldwide (Ferlay et al. 2004). In Germany, despite a declining incidence, esophagogastric adenocarcinoma still accounted for 12,300 cancer deaths in 2006 and 21,500 new annual cases are expected (www.rki.de). Most patients present with advanced or metastatic disease and about 75 % will ultimately require palliative treatment and will die of their disease.

Palliative chemotherapy prolongs survival (Wagner et al. 2006) and may maintain quality of life (Al-Batran and Ajani 2010) but median survival for patients with advanced or metastatic disease hardly exceeds 10 months in clinical studies (Cunningham et al. 2008; Al-Batran et al. 2008a, b). Palliative chemotherapy using 5-Fluorouracil (5-FU) derivatives (infusional 5-FU, capecitabine or S1) and platinum compounds (cis- or oxaliplatin) is regarded as standard of care but a universally accepted reference regimen cannot be defined (Cunningham et al. 2008; Al-Batran et al. 2008a, b; Kang et al. 2009). Docetaxel improved the activity of cisplatin and 5-FU combination and had positive impact on quality of life but toxicity was substantially increased (Van Cutsem et al. 2006; Ajani et al. 2007).

Regarding molecular-targeted agents, only trastuzumab has thus far shown improved overall survival and maintained quality of life in patients with human epidermal growth factor receptor 2 (HER2) positive metastatic esophagogastric adenocarcinoma (Bang et al. 2010; Shen et al. 2011). HER2 is a protein found on the surface of cancer cells (Höhler et al. 2010). Large amounts of HER2 can lead to malignant cellular growth. HER2-positive cancers are considered to be more aggressive and have been associated with poor survival in several albeit not all case series (Ananiev et al. 2011; Grabsch et al. 2010). Trastuzumab is a humanized monoclonal antibody targeting HER2. A large multicenter randomized controlled phase III trial (ToGA: **T**rastuzumab f**or** **GA**stric Cancer) investigated the addition of trastuzumab to standard capecitabine (or 5-FU)/cisplatin-based treatment in patients with HER2-positive tumors (Bang et al. 2010). HER2 positivity was defined as follows: either an immunohistochemistry (IHC) score of 3+ or a positive confirmation of gene amplification using in situ-hybridisation (ISH) techniques, here fluorescence ISH (FISH). ToGA revealed a significant benefit of 2.7 months in overall survival for the patient group treated with additional trastuzumab. Trastuzumab has been approved for the subgroup of patients deriving the greatest benefit in the ToGA trial (i.e., 4.2 months survival), namely patients with HER2 IHC 3+ *or* IHC 2+ and confirmatory ISH-positivity. In Germany, trastuzumab has been approved in January 2010 for the first-line treatment of HER2-positive esophagogastric adenocarcinoma in combination with capecitabine or 5-FU and cisplatin.

In this pooled analysis of data obtained with Therapiemonitor®, we focused on two aspects:

1. To describe treatment patterns in clinical practice and to elicit time trends in the choice of drugs and treatment intensity.
2. To investigate the implementation of HER2 testing (frequency and test algorithm) along with variables influencing likelihood of testing using bi- and multivariate analyses.

Materials and methods

Therapiemonitor and selection of centers

The methodology of Therapiemonitor® has been described in detail previously (Hofheinz et al. 2010). Briefly, clinical and epidemiological data of patients with metastatic esophagogastric adenocarcinoma undergoing treatment decisions within a defined time period in a representative sample of institutions are reported retrospectively.

The selection of centers for documentation follows a two-step procedure. The apportioned and stratified random sample is based on an initial survey among all institutions (about $n = 800$) dealing with the treatment of patients with advanced gastric cancer. According to this survey, the "treated prevalence" is ascertained and a collective of patients is apportioned according to treatment center and distributed regionally according to population density. In a second step, selected centers are asked to document their patients undergoing treatment decisions in the respective time period.

Physicians document treatment along with demographic- and tumor-related data, former medical and surgical treatment, insurance status, etc. Outcome data such as progression-free or overall survival are *not* collected. Data are centrally monitored and checked for plausibility and completeness.

Statistical analysis

All analyses presented in this report are explorative. Regarding the analysis of HER2 testing, we focused on non-study patients (NSP) only with metastatic esophagogastric adenocarcinoma. The percentage of patients undergoing HER2 testing was evaluated by dividing tested NSP by all NSP. The analysis of the correct application of HER2 testing was based on the test algorithms recommended by experts and the manufacturer (Rüschoff et al. 2010, 2012). All patients in whom the recommended algorithm was not followed were regarded as tested inaccurately.

In a first step, the impact of potentially relevant predictive factors (patient or tumor variables, treatment goals, type of test-initiating institution) on the likelihood of HER2 testing was assessed separately for each potentially relevant factor by using a two-sided chi-square test. A Fourfold Point Correlation between factors being significant at the 5 % significance level in the bivariate analysis was calculated, and only independent factors (correlation not higher than 0.5) were included in a multivariate logistic regression model (Kleinbaum et al. 1998). To define the best subset of predictive factors in the multivariate logistic regression model, forward variable selection procedure was used. Appropriateness of the resulting model was checked by using Hosmer–Lemeshow test and the rate of correct predictions.

In this model, all significant variables from the bivariate analyses were analyzed in a dichotomized format (binary variables). Further, a sensitivity analysis was done with a model including age, number of metastases and KPS as continuous variables.

For all comparisons, a p value of less then 0.05 was considered statistically significant. Analyses were performed using SPSS version 19.

Results

Patients and tumor characteristics

Patients and tumor characteristics are depicted in Table 1 separately for 2010 and for pooled data from the years 2006–2009 (already published, Hofheinz et al. 2010). A total of 861 patients with metastatic esophagogastric adenocarcinoma were documented in 2010 in two waves during quarter I/II and III/IV. Of these, 754 patients received first-line palliative chemotherapy in 2010. The remainder either underwent radiotherapy, resection of metastases, or was treated with best supportive care only. Thus, a total of 754 patients were subject to the analysis on drug use and treatment intensity. Median age of the patients was 67 years (range: 24–90 years). Fifty-eight percent were older than 65 years, and about two-thirds were male. Seventy-seven percentage of the patients had a Karnofsky performance status (KPS) $\geq$80 %. Regarding disease status, most of the patients (70.0 %) had been diagnosed with advanced disease. Liver metastases (62.0 %) and peritoneal carcinomatosis (45.7 %) were the most frequently reported sites of metastases. Majority of the patients were treated in non-university hospitals and private oncology practices (82 %).

Comparing the demographic and tumor characteristics of the patients documented in 2010 with the pooled data from 2006–2009, no differences were observed. In so far, the sample of patients documented in 2010 can be considered as representative and comparable with the patient sample analyzed in previous surveys.

Administered drugs and treatment intensity–trends over time

Data of 754 patients were available for analysis of administered drug and treatment intensity (i.e., use of monotherapy, doublet or triplet chemotherapy) in 2010. Table 2 provides an overview of the most frequently used cytotoxic drugs in 2010 as compared to previous years (n = 1,058 in 2006–2009).

Virtually all patients received fluoropyrimidine-based treatment in the first-line treatment. The oral 5-FU derivative capecitabine has increasingly been used over time with a total of 23.5 % of patients receiving capecitabine in 2010 as compared to 2009 (17.1 %). It is noteworthy that epirubicin (as part of ECF/EOF and ECX/EOX regimes) has also increasingly been used in 2010 (24.7 %) as compared to previous years.

Platinum derivatives were administered in 87 % of patients. An increased use of oxaliplatin was observed in 2010 with 37.9 % of the patients receiving oxaliplatin-based first-line treatment versus 23.8 % in 2006–2009. The use of docetaxel remained relatively stable in the range of 20–25 %.

Other and older drugs such as paclitaxel, etoposide, mitomycin C or irinotecan have almost completely disappeared from the therapeutic armamentarium in the first-line treatment of advanced esophagogastric adenocarcinoma.

The treatment intensity illustrated as the use of monotherapy, chemotherapy doublets and triplets or quartets over time is listed in Table 3. Of the patients, 6.1 % were treated with a monotherapy, 33.7 % with a doublet and 58.4 % with triplet in 2010. The trend to use more intensive first-line treatment observed already in previous documentation periods in 2008 and 2009 continued. In comparison with 2008 for instance, the percentage of

Table 1 Patient and tumor characteristics of patients ($n = 1{,}812$) with advanced or metastatic esophagogastric adenocarcinoma documented in Therapiemonitor® 2006–2010

	Total number of patients 2006–2009 *n* (%)	Total number of patients 2010 *n* (%)	I.–II. quarter 2010 *n* (%)	III.–IV. quarter 2010 *n* (%)
Total number of patients receiving palliative first-line CT/TT (n)	1,058	754	412	342
Gender[a]				
Male; *n* (%)	674 (63.8)	473 (62.7)	267 (64.8)	206 (60.2)
Female; *n* (%)	383 (36.2)	281 (37.3)	145 (35.2)	136 (39.8)
Age; median (years)	67	67	67	66.5
Range (years)	24–100	24–90	24–89	27–90
Patients aged <65 years (%)	44.7	42.3	44.4	42.7
Patients with KPS ≥80 % in first-line treatment (%)	72.9	77.5	78.7	75.8
Patients with initial diagnosis of carcinoma in stage IV (%)	69.8	70.0	70.6	69.3
Histology				
Signet cell cancer (%)	14.5	24.1	24.8	23.4
Undifferentiated cancer (G3) (%)	43.5	46.9	51.7	41.2
Metastatic sites[b]				
Liver (%)	50.1	62.0	58.8	65.9
Peritoneum (%)	43.2	45.7	46.3	45.1
Lung (%)	17.1	24.9	22.0	28.4
Bone (%)	8.5	10.0	9.5	12.8
Patients participating in clinical trials on first-line chemotherapy (%)	10.1	7.8	11.9	2.9
Treatment institution[b]				
University hospital	16.9	25.2	25.0	25.4
Other hospitals	59.7	52.4	50.5	54.7
Oncology practice	28.0	29.6	29.4	29.8
Insurance status				
Statutory insurance (%)	91.7	88.8	88.0	89.9
Private insurance (%)	8.3	11.2	12.0	10.1

CT chemotherapy; *KPS* Karnofsky performance status; *TT* targeted therapy

[a] Information on gender is missing in one patient

[b] Multiple answers were permitted

patients being treated with at least three active drugs has been almost doubled (30.5 % in 2008 versus 60.3 % in 2010). Contrarily, the percentage of patients receiving monotherapy has declined during the past years reaching a plateau of about 6 % in 2009 and 2010.

HER2 expression

Information on HER2 testing was available for a total of 861 patients documented in 2010, of which 64 were excluded because they participated in clinical trials. Thus, a total of 797 patients treated outside of clinical trials are available for the following analyses on HER2 testing. Out of these patients, 49.1 % ($n = 391$) were tested for HER2 expression as part of the therapy decision process. Sixty-one patients did either not undergo an IHC analysis ($n = 46$) or the testing method was not reported ($n = 15$) leaving a total of $n = 330$ patients with IHC analysis as a first step in HER2 testing.

Taken together, in 52.2 % of the tested 391 patients ($n = 204$), the suggested test algorithm was not applied in an appropriate manner. In 133 (34.0 %) patients with IHC 0, 1+, 3+ or unknown IHC-status an ISH analysis was carried out, while $n = 46$ patients (11.8 %) were diagnosed with ISH only. Ten patients with an IHC 2+ did not receive ISH analysis (3.1 %).

Regarding the test results in n= 330 patients with IHC as primary test method, the distribution of IHC scores was as follows: IHC 0 $n = 128$ (38.8 %), IHC 1 + $n = 98$ (29.7 %), IHC 2 + $n = 41$ (12.4 %), IHC 3 + $n = 54$ (16.4 %), unknown IHC $n = 9$ (2.7 %). Of $n = 41$ patients with IHC 2 +, $n = 17$ had a positive ISH analysis, $n = 13$

Table 2 Anti-cancer drugs used in the first-line treatment of patients advanced or metastatic esophagogastric adenocarcinoma ($n = 1812$) documented in Therapiemonitor® 2006–2010

	Total number of patients 2006–2009 *n* (%)	Total number of patients 2010 *n* (%)	I.–II. quarter 2010 *n* (%)	III.–IV. quarter 2010 *n* (%)
Cisplatin	538 (51.1)	370 (49.1)	218 (52.9)	152 (44.4)
Oxaliplatin	251 (23.8)	286 (37.9)	137 (33.3)	149 (43.6)
Capecitabine	133 (12.6)	177 (23.5)	88 (21.4)	89 (26.0)
Docetaxel	216 (20.5)	193 (25.6)	117 (28.4)	76 (22.2)
Paclitaxel	6 (0.6)	2 (0.3)	1 (0.2)	1 (0.3)
Irinotecan	92 (8.7)	31 (4.1)	17 (4.1)	14 (4.1)
Epirubicin	107 (10.2)	186 (24.7)	76 (18.4)	110 (32.2)
Mitomycin C	12 (1.1)	5 (0.7)	5 (1.2)	0 (0.0)
Etoposide	45 (4.3)	7 (0.9)	4 (1.0)	3 (0.9)
Evaluable patients (*n*)	1053	754	412	342

Indicated is the number of patients receiving the respective drugs in the respective years and/or quarters

Table 3 Treatment intensity in the first-line treatment of patients with advanced or metastatic esophagogastric adenocarcinoma ($n = 1{,}812$) documented in Therapiemonitor® (2006–2010)

	2008 (%)	2009 (%)	2010 (%)
Monochemotherapy	11.8	6.4	6.1
Chemotherapy doublet	57.7	46.6	33.7
Chemotherapy triplet	30.5	47.0	58.4
Chemotherapy quartet	–	–	1.9

Indicated is the percentage of patients receiving the respective treatment in the indicated years and/or quarters

Folinic acid is not considered an active drug and is consequently not included in this analysis

were negative, $n = 10$ were not tested and in one patient the result was not known.

Taken together, 71 out of 330 patients (21.5 %; $n = 54$ with HER2 3+ and $n = 17$ with IHC 2+/ISH+) fulfilled the criteria for HER2 positivity and were eligible for trastuzumab treatment according label. Of these patients, $n = 61$ were treated with trastuzumab in the first-line setting which equals 15.6 % of the tested patient group ($n = 391$), while $n = 10$ patients received other medical treatment.

Bivariate and multivariate analysis for HER2 testing

For the present analysis, patient- and tumor-specific as well as institutional-related variables (i.e., the decision-making institution) were recorded. Again, only patients not treated within clinical trials were included in the analysis. Several variables were found to be associated with HER2 testing (see Table 4). Lowest *p* values ($p < 0.001$) occurred for the following variables: Lower age (<67 years), higher KPS (>80 %) (see also Fig. 1), number of metastases,

Table 4 Chi-square test for variables with potential predictive value regarding the likelihood of HER2 testing

Variable	*p* value
Karnofsky performance status ≤80 versus >80	<0.001
Age <67 versus ≥67	<0.001
Localization of primary tumor: AEG versus other	0.355
Laurén classification: diffuse type versus other	0.191
Number of metastases: none/singular versus multiple	<0.001
Treated Concomitant disease: yes versus none	0.030
Objective of treatment: "resectability of the primary tumor": yes versus no	0.029
Objective of treatment: "prevention of progression": yes versus no	<0.001
Objective of treatment: "improvement of tumor-related symptoms": yes versus no	0.462
Objective of treatment: "maintenance of quality of life": yes versus no	0.199
Initiating institution: clinics yes versus no	0.026
Initiating institution: office yes versus no	0.003

Included in the analysis are only patients not participating in clinical trials ($n = 797$)

AEG adenocarcinoma of the esophagogastric junction

"prevention of progression" as objective of treatment. In addition, the initiating institutions office ($p = 0.003$) and clinics ($p = 0.026$) were significant. Fig. 2 shows the results of the bivariate analysis: The groups with a higher ratio with the HER2 testing are age <67 years, multiple metastases, "progress prevention" as therapeutic intention and KPS >80 % as well as treatment initiation in clinics. Contrarily, only a minority of patients with concomitant disease requiring treatment, "resectability of primary tumor" as treatment intention as well as treatment initiation by an office-based oncologist were tested for HER2.

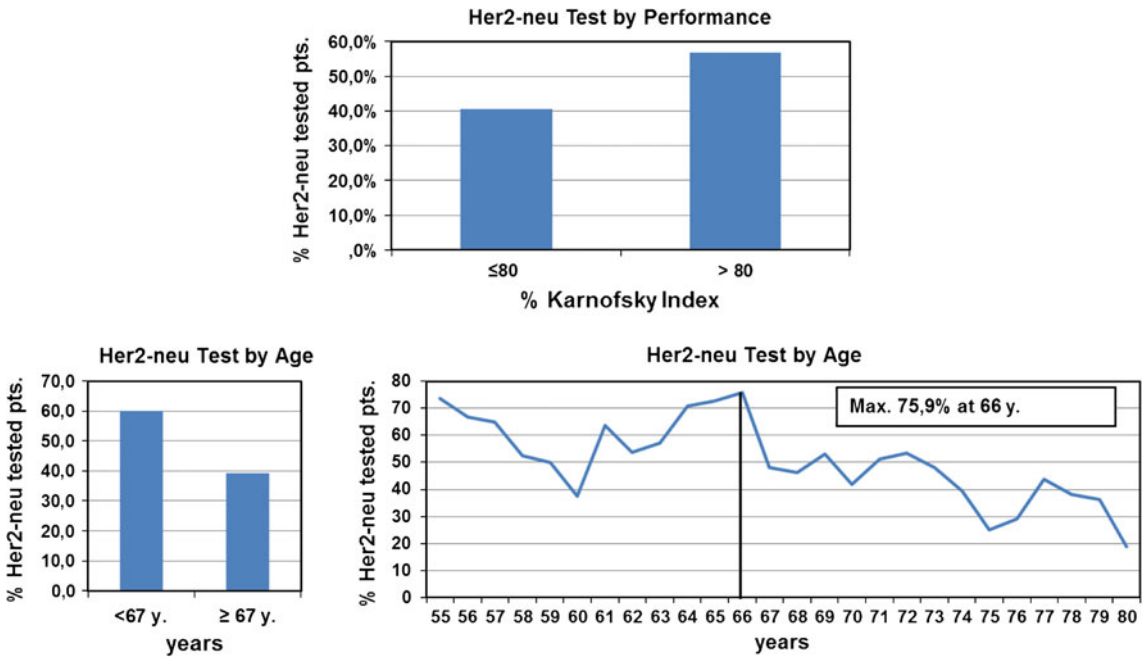


Fig. 1 HER2 testing as a function of Karnofsky performance status and age. Results of a bivariate analysis in patients with metastatic esophagogastric adenocarcinoma documented in Therapiemonitor 2010

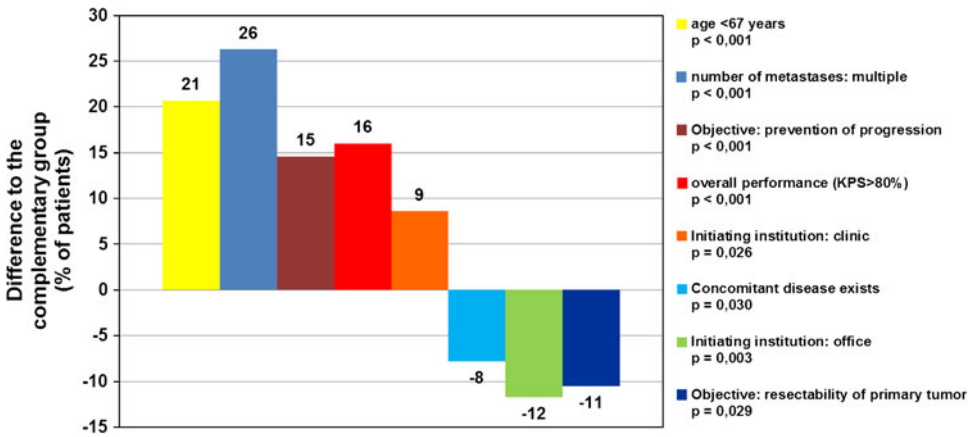


Fig. 2 Variables with significant positive or negative predictive value for HER2 testing results of a bivariate analysis in patients with metastatic esophagogastric adenocarcinoma documented in Therapiemonitor 2010. Indicated are the variables along with the difference (in % of patients) to the complementary group. *KPS*, Karnofsky performance status

Patient treated with the intention "prevention of progression" for instance had a higher chance (raised by 15 percentage points) of being tested for HER2 as the complementary group. The chance of being HER2 tested in patients with a higher number of metastases was even more pronounced (chance raised by 26 percentage points).

Using a Fourfold Point Correlation matrix, a possible correlation between the tested potentially relevant variables was investigated. Due to the high correlation between the variables "initiating institution clinics" and "initiating institution office only" the variable "initiating institution office" was included into the further analyses.

The observed differences regarding the test-initiating institution raised the question if the type of institution was applicable as an independent parameter influencing HER2 testing or if patients treated in practices differ regarding patient- or tumor-related variables from those treated in hospitals. Age distribution was comparable between both types of initiating institution. Patients treated in hospitals generally had better KPS (>80 %: 46 vs. 33 %; $p = 0.004$), but had more concomitant illness (61 vs. 41 %; $p < 0.0001$). Significant differences were observed regarding treatment intentions: "Maintenance of quality of life" (73 vs. 55 %; $p < 0.0001$), and "prevention of progression" (82 vs. 75 %; $p = 0.021$), was more frequently stated regarding patients treated in hospitals while "resectability of primary tumor" was more often indicated regarding patients in practices (42 vs. 13 %; $p < 0.0001$).

In summary, disparity between both institution types exists but this difference might not only explainable by patient-related KPS status or age. However, it may be better explained by the physician/institution determined "treatment goal" variables. Therefore, a variable defining the institution was included into further multivariate analysis.

As outlined in the "Materials and methods" section, a model was investigated using multivariate logistic regression analysis. In this model, significant variables from the bivariate analysis and with proven independency by Fourfold Point Correlation matrix were analyzed in a dichotomized format with a stepwise forward analysis. The variables age ≥67 years, "initiating institution office" had a negative impact on HER2 testing, while "prevention of progression", multiple metastases and a favorable KPS (>80 %) had a positive impact (see Fig. 3). For the resulting model, the probability of HER2 testing was correctly predicted in 65.6 % of all cases, respectively. Applying this model and using the formula shown in Fig. 4, the probability of HER2 testing can be calculated according to presence or absence of predictive factors. Examples on four parameter combinations are indicated. The highest probability of being tested for HER2 had younger patients (<67 years) with KPS >80 % and several metastases being treated in hospitals with the intention to prevent progression of disease. Patients fulfilling all five criteria had a likelihood of being tested of 87 % in the documented patient collective.

The model for the sensitivity analysis yielded the same significant variables and gave a comparable quota nearly the same quota of correct prediction (67.9 %).

Discussion

Therapiemonitor was developed and established as a healthcare research tool to collect and analyze data on treatment reality in patients with malignant diseases. Here, we report on 861 patients with metastatic esophagogastric adenocarcinoma documented in 2010 with Therapiemonitor. Notably, patient and tumor characteristics of this patient group compared well with previous years rendering the documented patient group a representative collective for the present analysis.

Regarding the use of cytostatics the trend to use oxaliplatin instead of cisplatin and capecitabine as substitute for 5-FU continued (Hofheinz et al. 2010). Docetaxel is also frequently used as first-line treatment, yet it exhibits a ceiling effect with about 25 % of patients being treated with this drug in the present collective. An intriguing finding of the present analysis is that treatment intensity, that is, the use of at least three active drugs is further increasing. A total of 60.3 % of patients was treated with triplets or quartets which represents a dramatic increase in comparison with 2006 (~10 %) and 2008 (~30 %) (Hofheinz et al. 2010). Interestingly, the percentage of a third drug nourishing 5-FU and platinum combinations is equally distributed between epirubicin (which has gained acceptance) and docetaxel. Most probably this intensification of treatment is due to the encouraging results of studies such as REAL2 (Cunningham et al. 2008), FLOT and FLOT65 + (Al-Batran et al. 2008a, b, 2009) the latter demonstrating that the addition of docetaxel was also worthwhile and feasible in some elderly patients with a median age of 70 years in conjunction with infusional 5-FU and oxaliplatin.

The main focus of the present analysis was the implementation of HER2 testing and trastuzumab use during the first year after approval (January 2010). Physicians were asked to report on the testing of HER2 regarding all first-line patients and the use of trastuzumab (if any). A main finding was that only 49.1 % of all patients were tested for HER2 in 2010. In only 52.2 % of these patients, the currently recommended test algorithm was applied (i.e., IHC first and in case of IHC 2 + →ISH analysis). It is of course difficult to judge the quality of testing, but the frequency of

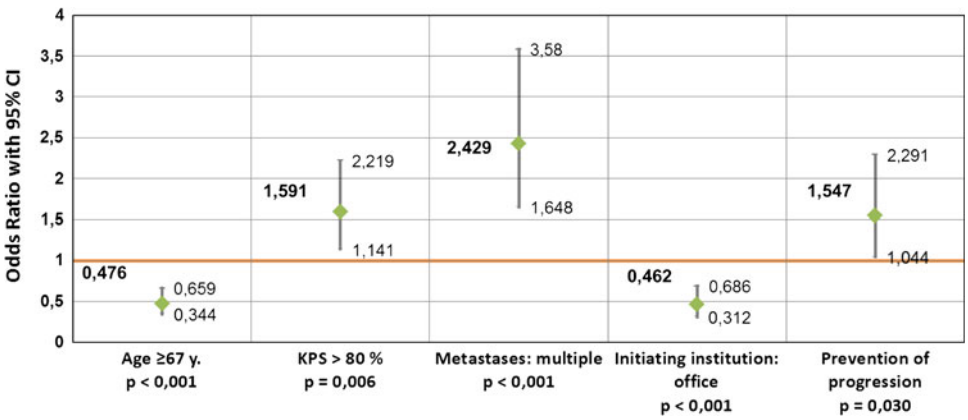
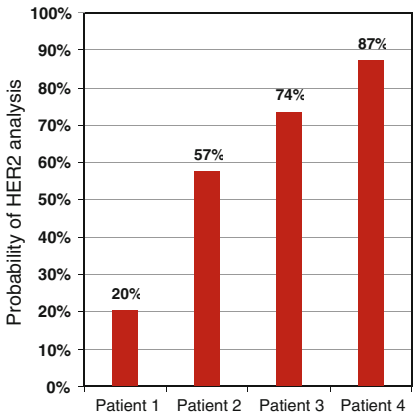


Fig. 3 Predictive factors for HER2 testing (stepwise forward logistic regression analysis) in patients with metastatic esophagogastric adenocarcinoma documented in Therapiemonitor 2010. Indicated are odds ratios (OR) together with 95 % confidence intervals indicating the odds (x-fold) of HER2 testing if the particular variable changes while all other variables remain unchanged. *KPS*, Karnofsky performance status

Model patients	Patient 1	Patient 2	Patient 3	Patient 4
Institution: office	yes	no	no	no
„Progress prevention“	no	yes	no	yes
Multiple metastases	no	no	yes	yes
Age ≥67 years	yes	yes	no	no
KPS >80%	no	yes	no	yes



Calculation of probabilities (logistic regression equation / results from regression coefficient):

L (Logit) = 0,143+ (m1pallokini_prax * -0,771) + (m1palzielverhprog * 0,436) + (m1_anzahl_metastasen * 0,887) + (altersplitgr66* -0,742) + (m1palkisplitgr80 * 0,464)

$$p = \frac{1}{1 + e^{-L}}$$

Fig. 4 Likelihood of HER2 testing in model patients according to presence or absence of predictive factors as determined in stepwise forward logistic regression analysis and formula for the calculation of probability for patients with metastatic esophagogastric adenocarcinoma documented in Therapiemonitor 2010. *KPS*, Karnofsky performance status

IHC subtypes and of HER2 positivity may serve as a clue. The HER2 overall positivity results of the present analysis are comparable with the ToGA trial (21.5 % in the present analysis and about 17 % in ToGA) if slightly higher in the present analysis maybe due to a higher proportion of patients with adenocarcinoma of the esophagogastric junction which are known to have a higher likelihood of HER2 positivity (38 % in the present patient group [data not shown] vs. 17–20 % in ToGA). Moreover, the distribution of IHC scoring between the present analysis and the ToGA screening study is comparable, as well (IHC 0/1 + 68.5 % present study vs. 76.8 % ToGA; IHC 2 + 12.4 % vs. 11.8 %, IHC 3 + 16.4 % vs. 11.4 %, IHC unknown 2.7 % vs. 0 %) (Bang 2009). Due to the low rates of testing for HER2 in our current analysis only 9 % of the patients documented in Therapiemonitor 2010 were eligible for first-line treatment with trastuzumab.

In view of this low rate of tested patients, we hypothesized that tumor- and patient-related variables exhibiting a low pre-test probability of HER2 positivity might have influenced testing strategies. From ToGA study, it was known that intestinal tumor type according to Laurén and AEG tumors show higher HER2 positivity rates (Bang 2009; Bang et al. 2010). We investigated potential predictive factors in a bivariate analysis. Interestingly, AEG tumors and tumor type according to Laurén had no impact on HER2 testing, whereas age <67 years, KPS >80 %, presence of multiple metastases, and “progress prevention” as therapeutic intention as well as treatment initiation in hospitals in contrast to office-based care did. Using multivariate logistic regression analysis, all five factors remained significant. These data raise several questions, firstly regarding the practice and test algorithms for HER2 analysis. During the first months of trastuzumab market approval, there was no commonly accepted test strategy and the currently proposed test algorithm was not universally adopted. Meanwhile, S3-guidelines underscore that the proposed algorithm should be applied and suggest to do HER2 analyses in qualified laboratories only (Moehler et al. 2011).

Secondly, patient- and tumor-related (age, KPS, metastatic load) as well as physician-related factors (therapeutic intention, institution) were identified as being predictive for HER2 testing. Especially, the fact that patients being treated in practices had a lower probability of being tested was surprising. It could be shown that this is not completely explainable by different patient profiles treated in practices versus hospitals. Apparently, also different treatment intentions impacted the likelihood of testing patients for HER2 analyses as well. It remains of course speculative if practical reasons such as access to tumor material and to pathology institutes offering high quality HER2 testing might have played a role during the first year after trastuzumab market approval.

In conclusion, the results of Therapiemonitor 2010 confirm the trend toward the use of more intensive treatments in the first-line setting in patients with esophagogastric adenocarcinoma. Moreover, during the first year after trastuzumab approval in 2010 several shortcomings were observed. Most strikingly a low testing rate for HER2 and an inaccurate use of the proposed test algorithm in a high percentage of patients were observed. Using multivariate logistic regression analyses, we identified clinical as well as physician-related factors which negatively impacted the

likelihood of testing patients for HER2. The present analysis illustrates that the results of clinical studies on *conventional* chemotherapies relative quickly impact treatment reality. On the other hand, it could be shown by means of the first year of trastuzumab that the implementation of a test-based treatment strategy bears several pitfalls. This data suggest that only increased joint interdisciplinary and intersectoral efforts will enable a quicker implementation of new molecular-targeted agents into standard diagnostic and treatment algorithms.

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