ELSEVIER

European Journal of Cancer 40 (2004) 1193–1198

European Journal of Cancer

www.ejconline.com

MAX2—a convenient index to estimate the average per patient risk for chemotherapy toxicity: validation in ECOG trials

M. Extermann[a,*], M. Bonetti[b], G.W. Sledge[c], P.J. O'Dwyer[d], P. Bonomi[e], Al.B. Benson III[f]

[a]*H. Lee Moffitt Cancer Center, University of South Florida, Tampa, FL, USA*
[b]*Harvard School of Public Health and Dana-Farber Cancer Institute, Boston, MA, USA*
[c]*Indiana University Medical Center, USA*
[d]*University of Pennsylvania Cancer Center, Philadelphia, PA, USA*
[e]*Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL, USA*
[f]*Northwestern University Medical School, The Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA*

Received 30 September 2003; accepted 12 January 2004

Abstract

Cancer patients, especially the elderly, present with a highly variable susceptibility to toxicity from chemotherapy. To estimate correctly a patient's risk for toxicity, both the average toxicity of a chemotherapy regimen and patient-related variables need to be assessed. However, treatment toxicities are typically reported item by item, not summarised per patient. We tested an index derived from a pilot study, the MAX2, on the ECOG database. Studies including 20 or more patients aged 70 years and older per arm were selected. Four studies were identified, representing 2526 patients, 410 (16%) being elderly. The association of the MAX2 index with the per patient incidence of grade 4 haematological and/or grade 3 or 4 non-haematological toxicity was highly significant, both for the overall group and for the elderly subgroup. The MAX2 index is a convenient and reproducible way of comparing the average per patient risk for toxicity from chemotherapy across several regimens.

Keywords: Chemotherapy toxicity; Aged; Aged >80 years; Predictive factors

1. Introduction

Oncologists are increasingly called to treat older patients. The challenge in treating this population is its highly variable health status. Therefore, reliable tools to predict the risk for toxicity from chemotherapy need to be developed. Toxicity is essentially dependent on two factors: the general toxicity of the chemotherapy regimen itself and various patient-related factors that may increase or decrease toxicity, such as comorbidity, functional status, depression, liver or kidney function [1,2]. Unfortunately, the toxicity from chemotherapy is mostly reported item by item and not summarised as a per patient risk for severe toxicity. In order to be realistic in daily practice, a predictive index should be patient-centred and valid across several chemotherapy regimens. Therefore, a way of 'summarising' and ranking the toxicity of various chemotherapies per patient is needed to create such an index. In a pilot study at H. Lee Moffitt Cancer Center, we demonstrated that: (1) both chemotherapy-related and patient-related factors had an independent measurable effect; (2) a simple index, called MAX2, seemed to be an effective way to summarise the toxicity of a given regimen, and was showing strong association with the degree of toxicity experienced by the patients [3]. We therefore decided to test the validity of the MAX2 on a larger scale in the Eastern Cooperative Oncology group (ECOG) trial database.

The construction of the MAX2 index has been described in detail elsewhere [3]. Its name derives from the fact that it considers the two most frequent severe toxicities reported: one haematological and one non-haematological. The way it is calculated is shown in

* Corresponding author. Tel.: +1-813-979-3822; fax: +1-813-972-8468.
E-mail address: extermann@moffitt.usf.edu (M. Extermann).

0959-8049/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2004.01.028

Table 1. After our 60-patient pilot study, two hypotheses could be made: either most of the patients experiencing severe toxicity from chemotherapy would experience one of the two most frequent toxicities included in the MAX2, in which case, the index would have a high association with the risk of severe toxicity; or severe toxicities would be experienced in a fairly random way, and therefore the MAX2 would have a lesser association with the risk of severe toxicity.

2. Methods

We extracted eligible studies from the ECOG trials database according to the following criteria: prospective phase II or III trials started after 1980; at least 20 patients aged 70 years and older per treatment arm; evaluation of toxicity according to NCI common toxicity criteria. Once a trial was identified, we reviewed individual toxicity data and extracted the table of the most severe toxicities per category (e.g. neutropenia, diarrhoea, neuropathy) and per patient. We repeated the analysis in the subgroup of patients aged 70 years and older. The MAX2 index was calculated for each treatment arm over all patients, as in Table 1. The association of the MAX2 index with the percentage of patients experiencing at least one grade 4 haematological and/or one grade 3 or 4 non-haematological toxicity (this combined endpoint will be referred to as 'severe toxicity') was evaluated using a simple linear-regression model and a logistic regression analysis. This toxicity endpoint was chosen because these are the grades of toxicities that prompt a treatment modification in most chemotherapy trials.

3. Results

Four trials met our eligibility criteria: a metastatic breast cancer trial (E 1193) [4], an advanced lung cancer trial (E 5592) [5,6], and two metastatic colon cancer trials (E 2290 and E6293) [7,8]. These trials included 2526 patients, 2515 eligible for analysis; 16% or 410 patients, were aged 70 years or older. Twelve different treatment regimens were tested (Table 2). The MAX2 of each regimen and the percentage of patients experiencing severe toxicity are presented in Table 3. Fig. 1 shows the results of fitting a simple linear-regression

Table 1
The MAX2 index[a]

$$\frac{\text{Most frequent grade 4 haematological toxicity} + \text{most frequent grade 3+4 non-haematological toxicity}}{2}$$

Example
25% grade 4 neutropenia $\text{MAX2} = \frac{0.25 + 0.13}{2} = 0.19$
13% grade 3+4 diarrhoea

Notes
Alopecia is not counted
When only white blood cell nadirs are reported, ANC is extracted as follows:
0.6* G3+4 leucopenia, if G4 leukopenia <30%
0.8* G3+4 leucopenia, if 30% and above

[a] An index that allows adjustment for the toxicity of different chemotherapy regimens for comparison [3].

Table 2
Trials' characteristics

Trial	No. of patients	No. 70 years and older	Regimen used	Doses (mg/m^2)
E1193	739	69 (9%)	Doxorubicin	60
			Paclitaxel	175–3 h
			AT + G-CSF	50/150-3 h + G-CSF
E2290	1099	230 (21%)	5-FU	2600–24 h
			PALA-5-FU	550/2600–24 h
			5-FU-LV oral	600/125
			5-FU-LV intravenous	500/500
			5-FU-IFN-α	750/9 MIO
E5592	588	87 (15%)	Cisplatin-etoposide	75/100×3
			Cisplatin-paclitaxel 250	75/250–24 h + G-CSF
			Cisplatin-paclitaxel 135	75/135–24 h
E6293	100	24 (24%)	Raltitrexed	3
All	2526	410 (16%)		

AT, doxorubicin-paclitaxel; 5-FU, 5-fluouracil; G-CSF, granulocyte-colony-stimulating factor; LV, leucovorin; IFN, interferon.

Table 3
MAX2 and percentage of patients experiencing severe toxicity

Study	Regimen	MAX2	Risk of toxicity	Risk in patients >70 years
E1193	Doxorubicin	0.26	0.66	0.75
	Paclitaxel	0.42	0.86	0.95
	AT + G-CSF	0.30	0.72	0.95
E2290	5-FU	0.07	0.34	0.37
	PALA-5-FU	0.03	0.37	0.42
	5-FU intravenous	0.17	0.49	0.55
	5-FU-interferon-α-LV orally	0.19	0.50	0.51
	5-FU-LV	0.12	0.53	0.64
E5592	Cisplatin-etoposide	0.38	0.76	0.95
	Cisplatin-paclitaxel 250	0.47	0.90	0.91
	Cisplatin-paclitaxel 135	0.50	0.90	1.00
E6293	Tomudex	0.14	0.42	0.33

AT, doxorubicin-paclitaxel; 5-FU, 5-fluouracil; G-CSF, granulocyte-colony-stimulating factor; LV, leucovorin.

model to the individual observations to describe the association between MAX2 and the incidence of severe toxicity. The linear-regression equation is Prob = 0.30 + 1.26×MAX2 for all patients and Prob = 0.33 + 1.38× MAX2 for elderly patients. The R^2 from the two regressions were 0.16 and 0.20. Note that fitting a simple linear regression to binary data is possible if the probabilities are far enough from the extreme values of zero and one, as a logistic curve is likely to be sufficiently linear in the range of interest. The regression should be fit using unweighted least squares on the individual observations. The R^2 obtained from such a regression should, however, be interpreted with caution, as the binary nature of the outcome variable is such that the maximum possible R^2 is likely to be much smaller than one, as shown by Cox and Wermuth [9]. In our setting, the data are such that the conditional probability of toxicity is approximately uniformly distributed in the range (0.3, 0.9) ((0.3, 1) for the elderly). By following the arguments of Cox and Wermuth [9], one can show that in this condition the maximum possible R^2 in the two groups are approximately 0.22 and 0.26. In other words, the R^2 found in this study correspond to 73% and 77% of the maximum possible.

Fig. 2 shows the results of fitting the more refined logistic-regression model, separately for the whole group of patients and for the elderly subgroup. The fitted logistic-regression equations were

$$\text{Prob} = \frac{\exp(-0.94 + 6.16 * \text{MAX2})}{1 + \exp(-0.94 + 6.16 * \text{MAX2})}$$

for all patients and

$$\text{Prob} = \frac{\exp(-0.946 + 8.30 * \text{MAX2})}{1 + \exp(-0.96 + 8.30 * \text{MAX2})}$$

for patients aged 70 and above.

All parameters for both regressions were highly significant ($P < 0.001$). The residual deviance for the two models is equal to 18.94 and 22.85, respectively (both with 10 degrees of freedom), corresponding to P-values of 0.04 and 0.01, respectively. This indicates that even though the fit appears to be rather informative (see Fig. 2), it can be improved substantially by the inclusion of treatment-specific or patient-specific characteristics. Fitting of a logistic regression on all patients with the addition of a covariate measuring the proportion of elderly (>70 years) in each treatment arm did not improve the fit (goodness-of-fit P-value = 0.03).

Overall, there was no significant difference in the incidence of toxicity between elderly and younger patients: 0.64 (95% confidence interval (CI) 0.60–0.69) versus 0.63 (95% CI 0.61–0.65) ($P = 0.54$). It should, however, be noted that there was some heterogeneity between studies. In the lower range of toxicities the results were closer between subgroups, whereas at the upper end the older subgroups tended to have higher incidences of toxicity.

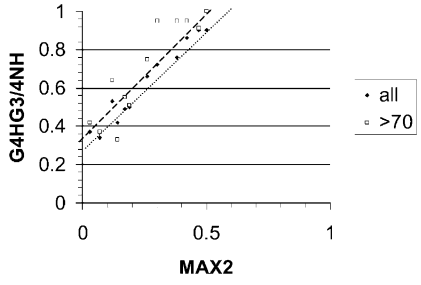

Fig. 1. Association between MAX2 and incidence of severe toxicity: linear regression. Comparison between the whole group (regression line dotted) and patients 70 years and older (regression line dashed).

4. Discussion

This study demonstrated the high association between the MAX2 index and the global incidence of severe

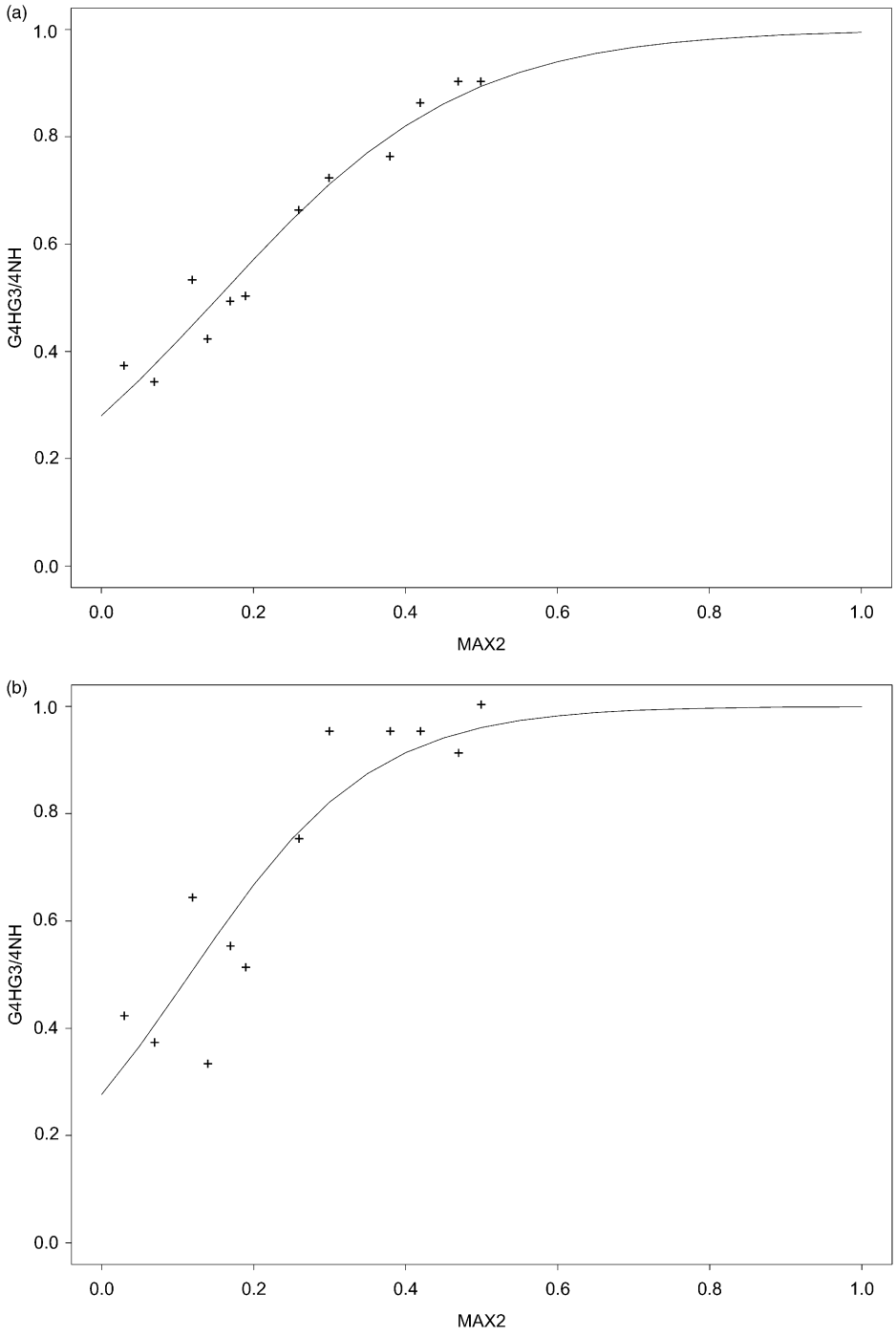

Fig. 2. Association between MAX2 and incidence of severe toxicity: logistic regression (a) all patients, (b) elderly patients.

toxicity from a chemotherapy regimen. This confirms the data from our pilot trial [3]. We were able to extract a regression equation that can be used to estimate the probability of toxicity from a published regimen. This index will also be a very helpful instrument in studies comparing the toxicity of several regimens. It will notably allow the development of an individualised risk score valid across several chemotherapy regimens, integrating also patient-related variables. Having a single index applicable to several regimens will certainly be most helpful in daily clinical practice. It should be noticed that in our analysis above for the elderly groups we used MAX2 that had been computed on the whole patient population, and not on the elderly only.

To confirm the validity of the index, two other elements can be explored. How stable is the index across several publications of a same regimen? And how sensitive is the index to modifications of the dose of a chemotherapeutic agent? To address these questions, we reviewed recently published studies with regimens

Table 4
Comparison with published data

This study	No. of patients (all ages)	MAX2 study	MAX2 published	Published comparison regimen	No. of patients (all ages)	Reference
AT 50/150	246	0.30	0.42	AT 50/220	134	[14]
5-FU/LV 500/500	224	0.19	0.14	5-FU/LV 500/500	148	[18]
Cisplatin/taxol	195	0.50	0.49	Cisplatin/taxol	201	[13]
75/135-24h			0.49	75/135–24 h	44	[19]
Cisplatin/taxol 75/250–24 h + G-CSF	197	0.47	0.49	Cisplatin/taxol 75/200–24 h + G-CSF	44	[20]
Cisplatin-etoposide 75/100×3	196	0.38	0.26	Cisplatin-etoposide 80/80×3	26	[9]

AT, doxorubicin-paclitaxel; , 5-fluouracil; G-CSF, granulocyte-colony-stimulating factor; LV, leucovorin.

comparable to the ones studied here. The results are presented in Table 4. It can be seen that MAX2 is well reproducible across studies. The toxicity of chemotherapy seems also to be rather stable across various types of tumour. For example, the MAX2 of gemcitabine given as 1.25 g day 1,8,15 q4 weeks is 0.03 and 0.09 in non-small cell lung cancer, 0.065 in non-Hodgkin's lymphoma, and 0.07 in Hodgkin's disease [10–13]. Results from studies with cisplatin-etoposide demonstrate a dose sensitivity (Table 4).

Some limitations apply to this index. The first is that it has only been validated with well-defined modern toxicity rating systems, such as the NCI common toxicity criteria or the World Health Organisation toxicity criteria. Caution should be paid to the definition of toxicity used by individual studies, notably those published before the mid-1990s. The definition of grade 4 neutropenia as <500 is, for example, crucial. Additionally, major changes in supportive regimens may affect the MAX2. For example, the introduction of 5-hydroxytryptamine$_3$ inhibitors around 1990 dramatically decreased the incidence of severe nausea, asking for caution in interpreting results from trials started before this date. The MAX2 also provides a global picture of the toxicity risk. It is not intended to replace the reporting of specific toxicities, which are very important to recognise in clinical practice. The extraction of the MAX2 is dependent of a structured description of the toxicities. This is not always available in published studies. Editors and authors should strive to present tables detailing each grade of at least the most frequent toxicities (such as in e.g. Refs. 14 and 15).

As noted above, there was no overall difference in toxicity between older and younger patients. Since these are cooperative group trials, the elderly patients enrolled are likely to have been selected healthy elderly. However, there is a trend in the upper range of toxicities toward a higher incidence in older patients. Larger numbers of patients will need to be studied to achieve a firm conclusion. Some confounding may also come from individual patient factors, which would be consistent with the results of our pilot, where individual patient-related factors were associated with toxicity independently from MAX2 [3]. This, together with the room for improving the fit of the models, again suggests that the construction of an individualised risk score with both chemotherapy and patient-related variables should also be pursued. Such a project is being undertaken at present. It should also be noted that despite the high incidence of severe toxicity, elderly patients appear to tolerate chemotherapy rather well in terms of function [16,17].

In conclusion, the MAX2 is a very reliable way of summarising the toxicity from a chemotherapy regimen on a per patient basis. It can be used in models to analyse this toxicity, or to control for this variable in the analysis of cancer databases.

Acknowledgements

Partial presentation of these results was made at the ASCO conference and the SIOG conference in 2002.

References

1. Frasci G, Lorusso V, Panza N, *et al*. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2000, **18**, 2529–2536.
2. Freyer G, Le Roi A, Weber B, *et al*. Geriatric evaluation and feasibility of platin-based first-line chemotherapy in elderly patients with advanced ovarian cancer. *Proc Annu Meeting Am Soc Clin Oncol* 2002, **21**, 359a.
3. Extermann M, Chen H, Cantor AB, *et al*. Predictors of tolerance to chemotherapy in older cancer patients: a prospective pilot study. *European Journal of Cancer* 2002, **38**, 1466–1473.
4. Stender MJ, Neuberg D, Wood W, Sledge G. Correlation of circulating c-erb B-2 extracellular domain (Her-2) with clinical outcome in patients with metastatic breast cancer (MBC). *Proc Annu Meet Am Soc Clin Oncol* 1997, **16**, A541.
5. Johnson DH. Phase III trial (E5592) comparing cisplatin plus etoposide with cisplatin plus paclitaxel at two dose levels for treatment of advanced non-small-cell lung cancer. Eastern Cooperative Oncology Group. *J Natl Cancer Inst Monogr* 1995, **19**, 61–63.
6. Bonomi PD, Kim K, Fairclough D, *et al*. Comparison of survival and quality of life in advanced non-small cell lung cancer patients treated with paclitaxel-cisplatin versus etoposide-cisplatin: results of an Eastern Cooperative Oncology Group Trial. *J Clin Oncol* 2000, **18**, 623–631.

7. O'Dwyer PJ, Manola J, Valone FH, *et al*. Fluorouracil modulation in colorectal cancer: lack of improvement with PALA or oral leucovorin or interferon, but enhanced therapeutic index with weekly 24-hour infusional schedule. An ECOG/CALGB study. *J Clin Oncol* 2000, **19**, 2413–2421.
8. Zalcberg JR, Ibrahim J, Johnston PG, *et al*. ECOG phase II study of Tomudex in advanced colorectal cancer. *Abstract and Presentation, American Society of Clinical Oncology* 1997, **16**, 268a.
9. Cox DR, Wermuth N. A comment on the coefficient of determination for binary responses. *The American Statistician* 1992, **46**, 1–4.
10. Perng RP, Chen YM, Ming-Liu J, *et al*. Gemcitabine versus the combination of cisplatin and etoposide in patients with inoperable non-small-cell lung cancer in a phase II randomized study. *J Clin Oncol* 1997, **15**, 2097–2102.
11. Fossa A, Santoro A, Hiddemann W, *et al*. Gemcitabine as a single agent in the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 1999, **17**, 3786–3792.
12. Santoro A, Bredenfeld H, Devizzi L, *et al*. Gemcitabine in the treatment of refractory Hodgkin's disease: results of a multicenter phase II study. *J Clin Oncol* 2000, **18**, 2615–2619.
13. van Putten JW, Baas P, Codrington H, *et al*. Activity of single-agent gemcitabine as second-line treatment after previous chemotherapy or radiotherapy in advanced non-small-cell lung cancer. *Lung Cancer* 2001, **33**, 289–298.
14. Muggia FM, Braly PS, Brady MF, *et al*. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. *J Clin Oncol* 2000, **18**, 106–115.
15. Jassem J, Pienkowski T, Pluzanska A, *et al*. Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. *J Clin Oncol* 2001, **19**, 1707–1715.
16. Chen H, Cantor A, Meyer J, *et al*. Can older cancer patients tolerate chemotherapy? A prospective pilot study. *Cancer* 2003, **97**, 1107–1114.
17. Watters JM, Cripps MC, O'Rourke K, *et al*. Functional status is well maintained in older patients undergoing adjuvant therapy for colorectal cancer. *Proc Annu Meeting Am Soc Clin Oncol* 2002, **21**, 365a.
18. Jager E, Heike M, Bernhard H, *et al*. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. *J Clin Oncol* 1996, **14**, 2274–2279.
19. Rose PG, Blessing JA, Gershenson DM, McGehee R. Paclitaxel and cisplatin as first-line therapy in recurrent or advanced squamous cell carcinoma of the cervix: a gynecologic oncology group study. *J Clin Oncol* 1999, **17**, 2676–2680.
20. Wasserheit C, Frazein A, Oratz R, *et al*. Phase II trial of paclitaxel and cisplatin in women with advanced breast cancer: an active regimen with limiting neurotoxicity. *J Clin Oncol* 1996, **14**, 1993–1999.