Tumor Burden Increase at Radiological Disease Progression Associates with Poor Overall Survival in Advanced Colorectal Cancer

Yuri Kogan, Moran Elishmereni, Eldad Taub, Zvia Agur

Optimata Ltd. Israel

Background

Investigating the association between quantifiable features of tumor burden and survival in advanced cancer patients can uncover elements whose control could potentially influence life expectancy in these patients.

Our aim was to examine how changes in tumor burden, and specifically in sum of longest diameters (SLD) during RECIST-determined progression (i.e. progressive disease, PD) could affect the post-progression survival (PPS) of patients with advanced colorectal cancer (CRC), using proportional-hazards survival models.

Methods & Results

Individual data of metastatic CRC patients under standard-of-care therapy were obtained from 3 clinical studies (accessible via projectdatasphere.org; Tab. 1).

The following factors (covariates) were evaluated as PPS predictors:

- **Baseline covariates**: Gender, age, weight, ECOG performance status, liver/lymph node metastases, histological grade, KRAS mutational status, baseline SLD.

- **Progression-related covariates**: 1. Time to progression (TTP); 2. Nature of the progression (target, non-target, and/or new-lesion PD); 3. Quantitative progression-SLD metrics capturing the tumor burden increase during PD (calculated only in patients uncensored for progression and with measurable tumor burden at RECIST-determined progression).

Univariate Analysis

The correlation of progression-associated covariates with survival in different CRC patient groups was examined by (1) univariate Cox proportional-hazards (PH) models, and (2) Kaplan-Meier plots (PPS curve separation assessed by the log-rank test).

The SLD change from nadir to PD (∆SLDP) was a significant predictor of PPS in CRC patients under 1st/2nd line treatment (Tab.2)

- Patients with small (∆SLDP < 1.5) had a 1.5-2 times longer survival than large-∆SLDP, patients in all groups (Fig.1)

Multivariate Analysis

Multivariate analysis was performed to test whether change in SLD from nadir to PD is an independent predictive factor for PPS. Thus, optimally sparse Cox PH models for PPS were built for each dataset and patient group, and the effect of adding ∆SLDP, was tested through HR, p value and the model Akaike information criterion (AIC) value (Fig.2).

The SLD change from nadir to PD (∆SLDP) remained an important PPS predictor in multivariate models controlling for other prognostic factors, including ECOG, TTP, KRAS, etc. (Tab. 3), and its addition improved the model AIC in every patient group and treatment line

The predictive power of ∆SLDP is apparent even in models with correlated covariates, e.g. SLD-BL as seen in models containing the residual of its regression on all other factors (Tab. 3)

In the 2nd line cohort, SLD-BL (baseline tumor size at 2nd line onset, at the end of 1st line) was the most significant PPS predictor (Tab. 3), stressing the importance of the SLD change at progression during 1st line therapy for survival.

Conclusions and Implications

- The increase in tumor size from nadir to progression (∆SLDP) is a survival predictor in CRC patients; its predictive power appears independent of the treatment line and drug applied to the patients.

- ∆SLDP is an independent significant predictor of survival, also when considered relatively to other disease predictors.

- This complements our past discovery that survival in metastatic non-small cell lung cancer is correlated with ∆SLDP [1], suggesting the cross-indication prognostic value of this factor.

- A potential implication: identification of impending progression at the right time, when the tumor increase is still small, could enable oncologists to effectively extend the patient’s survival (e.g. by an earlier switch to next-line therapy). This possibility must be prospectively tested.


Clin Oncol 16, 2018 (suppl. 01) 116

Website: www.optimata.com

Correspondence: yurikogan@optimata.com

Tab. 1. Univariate Cox regression of PPS on all tested factors. Progression-SLD metrics (red) and other covariates (black) were tested in all progressing patients (ALL-PD) or only target-lesion-progressing patients (TL-PD) in 2nd line settings. Hazard ratios (HR) and corresponding p-values are displayed. Significant covariates (p<0.05) are highlighted.

• Baseline SLD, ECOG performance status, presence of liver metastasis and high grade histology (poorly differentiated CRC) were also strong PPS predictors (Tab.2).

- Progression-SLD metrics were highly correlated between them, as well as with SLD-BL and ProgTL (not shown). Next, we proceeded to investigate ∆SLDP, as the representing progression-SLD metric in the multivariate model.

Fig. 1. Kaplan-Meier survival plots for ∆SLDP, dichotomized relative to its median, in patients with any progression type (ALL-PD) or target-lesion progression only (TL-PD) in each dataset. The median values separating the plots are shown for each group, along with corresponding p-values. The mean PPS is indicated in each curve.

Fig. 2. Approaches for the multivariate model development.

1. For a predictor and its second-order interaction terms. For a variable that was used in a previous step, the variable's AIC was recalculated in the presence of the predictor that is now tested.

2. Construction of a basic multivariate Cox model for PPS (PL) was followed by adding ∆SLDP to the model and by adding other variables with a p-value threshold of 0.05.

3. The resulting ∆SLDP model was constructed by backward stepwise elimination of covariates with a p-value threshold of 0.05.

4. The progression-SLD metrics (red) and other covariates (black) were tested in all progressing patients (ALL-PD)Leukemia and Lymphoma, 2018 (2018). www.optimata.com

Fig. 3. Correlation matrix for significant PPS covariates (n=19) in the univariate Cox regressions in ALL-PD and TL-PD patients (Tab. 2).

Tab. 2. Univariate Cox regression of PPS on all tested factors. Progression-SLD metrics (red) and other covariates (black) were tested in all progressing patients (ALL-PD) or only target-lesion-progressing patients (TL-PD) in 2nd line settings. Hazard ratios (HR) and corresponding p-values are displayed. Significant covariates (p<0.05) are highlighted.

• Baseline SLD, ECOG performance status, presence of liver metastasis and high grade histology (poorly differentiated CRC) were also strong PPS predictors (Tab.2).

- Progression-SLD metrics were highly correlated between them, as well as with SLD-BL and ProgTL (not shown). Next, we proceeded to investigate ∆SLDP, as the representing progression-SLD metric in the multivariate model.

Fig. 1. Kaplan-Meier survival plots for ∆SLDP, dichotomized relative to its median, in patients with any progression type (ALL-PD) or target-lesion progression only (TL-PD) in each dataset. The median values separating the plots are shown for each group, along with corresponding p-values. The mean PPS is indicated in each curve.

Fig. 2. Approaches for the multivariate model development.

1. For a predictor and its second-order interaction terms. For a variable that was used in a previous step, the variable's AIC was recalculated in the presence of the predictor that is now tested.

2. Construction of a basic multivariate Cox model for PPS (PL) was followed by adding ∆SLDP to the model and by adding other variables with a p-value threshold of 0.05.

3. The resulting ∆SLDP model was constructed by backward stepwise elimination of covariates with a p-value threshold of 0.05.

4. The progression-SLD metrics (red) and other covariates (black) were tested in all progressing patients (ALL-PD)Leukemia and Lymphoma, 2018 (2018). www.optimata.com

Fig. 3. Correlation matrix for significant PPS covariates (n=19) in the univariate Cox regressions in ALL-PD and TL-PD patients (Tab. 2).