Does Rapid Drug Desensitization to chemotherapy affect survival outcomes?

Short title: Rapid Drug Desensitization and Survival

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Abstract

Background: Oxaliplatin hypersensitivity reactions may affect prognosis by jeopardizing the timely completion of the scheduled treatment sessions, or by forcing reactive patients into unexpected changes in therapy. Rapid Drug Desensitization (RDD) allows these patients to safely receive their first-choice treatments. However, the possible effects of RDD on the efficacy of oxaliplatin has never been studied.

Objective: The objective of this study is to evaluate the effect on survival rates of RDD in oxaliplatin-hypersensitive patients**.**

Methods: 7-year retrospective study comparing survival between oxaliplatin-hypersensitive case patients (receiving oxaliplatin by RDD) and non-allergic control patients (receiving standard oxaliplatin infusions). The primary endpoint of this study was Overall Survival (OS) in cases and controls (Kaplan-Meier method with log-rank test comparisons).

Results: OS was 23.7 months (95%CI:15.3-30.9) for the 67 cases who underwent 337 RDDs, while for controls (n=143) it was 34.5 months (95%CI:21.7-55.5). There were no significant differences between both groups (HR1.42;95%CI:0.93-2.17;p=0.104).

Conclusions: Survival outcomes of oxaliplatin-hypersensitive patients who received oxaliplatin via RDD were not significantly different compared to those of control patients who received oxaliplatin via standard administration. Receiving oxaliplatin by means of RDD might be an effective therapeutic alternative for oxaliplatin-hypersensitive patients.

Key words: Drug allergy, Desensitization, Survival study, Hypersensitivity, Oxaliplatin, Skin test, Drug provocation test, Chemotherapy.

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Resumen

Antecedentes: Las reacciones de hipersensibilidad al oxaliplatino podrían afectar al pronóstico vital cuando fuerzan a los pacientes a cambiar de tratamiento o cuando impiden que lo finalicen. La desensibilización rápida medicamentosa permite que estos pacientes reciban sus tratamientos de primera elección. Sin embargo, no existen datos sobre si la desensibilización rápida medicamentosa podría tener algún efecto sobre la eficacia del oxaliplatino.

Objetivo: El objetivo de este estudio es evaluar los efectos que la desensibilización rápida medicamentosa al oxalipatlino pudiera tener sobre la eficacia del tratamiento en los pacientes alérgicos al oxaliplatino sometidos a desensibilización.

Métodos: Estudio retrospectivo comparando datos de supervivencia, durante un periodo de 7 años, entre pacientes de pacientes alérgicos al oxaliplatino (recibiendo oxaliplatino mediante desensibilización rápida medicamentosa) y controles no alérgicos (recibiendo administraciones estándar de oxaliplatino). La supervivencia global se seleccionó como el criterio de valoración de la eficacia principal y se analizó con el estimador Kaplan-Meier utilizando comparaciones mediante la prueba de log-rank.

Results: La supervivencia global de los 67 casos fue de 23,7 meses (95%CI:15,3-30,9), que se sometieron a 337 desensibilizaciones rápidas medicamentosas. Para los 143 controles la supervivencia global fue 34,5 meses (95%CI:21,7-55,5). No se encontraron diferencias significativamente estadísticas entre ambos grupos (HR1,42;95%CI:0,93-2,17;p=0,104).

Conclusions: Los resultados de supervivencia de los pacientes sometidos a desensibilización no fueron significativamente distintos a los de los controles que recibieron oxaliplatino de forma estándar. La desensibilización se presenta como una alternativa para recibir oxaliplatino de forma eficaz en pacientes alérgicos.

Palabras clave: Alergia a medicamentos, Desensibilización, Estudio de supervivencia, hipersensibilidad, Oxaliplatino, Pruebas cutáneas, Provocación controlada, Quimioterapia.

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Introduction

Colorectal cancer is the third most common cancer in men, and the second in women. The worldwide prevalence in 2012 was over 1,300,000 affected patients. About 20% of cases are diagnosed at an advanced stage, with a relative 5-year survival rate of approximately 11-12%**[1,2].** Standard treatment for these patients includes oxaliplatin-based chemotherapy regimes**[3].**

Drug hypersensitivity reactions (DHRs) to oxaliplatin have been reported with increasing incidences, and 21-37% of them might be severe**[4-6]** Because they usually appear after a median of 8 uneventful administrations**[4-6]**, these DHRs may jeopardize the completion of the scheduled treatment sessions, or they might force patients into unexpected changes in therapy when they are already succesfully receiving a standard oxaliplatin-based chemotherapy. Thus, DHRs to antineoplastic agents like oxaliplatin may lead to first-choice drug avoidance, and this avoidance could negatively affect prognosis[**4-16**].

Our group at Ramon y Cajal University Hospital (RCUH) has previously validated skin testing, specific IgE, and drug provocation testing (DPT) for the diagnosis of oxaliplatin DHRs**[6].** DPT involves the controlled administration of a drug to study DHRs, and it is considered to be the Gold Standard for establishing or excluding a diagnosis of drug hypersensitivity**[5,6,17].** DPT is a useful tool to rule out the diagnosis of hypersensitivity in a considerable percentage of patients and therefore to prevent non-hypersensitive patients from unnecessary desensitizations**[6].**

Recently our RCUH/RDD protocol was validated in a large cohort study**[5].** Rapid Drug Desensitization (RDD) is a therapeutic technique for drug allergy which allows allergic patients to receive a drug they are hypersensitive to. RDD induces a temporary state of tolerance to a drug responsible for a proven DHR, by means of the administration of progressively increasing doses of the culprit drug in a step-wise manner which has been previously validated in vivo and in vitro**[5,7-15].** Thus, RDD allows reactive patients to safely receive their first-choice treatments**[5-15]**. However, survival data on patients receiving oxaliplatin by means of RDD have not been reported.

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The primary objective of this study is to evaluate whether there are any effects of RDD on the survival rates of oxaliplatin-hypersensitive patients.

The secondary objective is to describe relevant data on the management of these patients, especially focusing on the role of DPT and the efficacy and safety of RDD.

Methods

Study Design

Retrospective analysis comparing survival data of oxaliplatin-hypersensitive cases receiving oxaliplatin by RDD and non-allergic controls receiving standard oxaliplatin infusions.

Study Population

Patients with advanced colorectal cancer (stage IV) reacting to oxaliplatin and included in the patient cohort of the Desensitization Program at RCUH during a 7-year period (between May 2009 and May 2016).

Allergy workup

As in previous works by our group**[5-12]**, all referred patients underwent systematic allergy study by means of: clinical history, severity classification according to a classification by Brown**[18]**, skin testing (ST), blood testing (including oxaliplatin-specific IgE and tryptase), risk-assessment, and drug provocation testing (DPT) whenever possible according to risk-assessment. **Figure 1.**

Skin Testing (ST) and specific IgE

ST was performed following standard international methodology**[5-7,19,20**] and in a dedicated space given the risk of anaphylaxis**[21].** ST were asessed according to international guidelines, as reported in previous articles by our group**[5-12,19].** Concentrations used for skin prick testing (SPT) were 5 mg/ml and 0.5 mg/ml. For intradermal testing (IDT) we only considered the 0.5 mg/ml

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concentration, given that we found false-positive results when using 5 mg/ml for IDT**[6].**

Oxaliplatin-specific IgE was determined by ImmunoCAP (Thermo Fisher Scientific Waltham, MA USA). Data from previous studies suggest 0.35 KU/l is the ideal cut-off point in our population**[6].**

Drug Provocation Test (DPT)

DPT is a helpful but risky technique that should only be performed by expert Allergists in adequate settings after careful risk-assessment. DPT consisted on administering the next scheduled treatment with the culprit drug following the same detailed recommendations described in recent articles by our group**[5,6,10].**

Criterion Standard for Final Diagnosis in this study

Criterion standard for a positive final diagnosis of hypersensitivity in this study: An unequivocal Clinical History was not considered suficient**[5-12]**, patients needed to also show Positive ST and/or positive DPT and/or positive oxaliplatin-specific IgE.

Criterion Standard for a negative final diagnosis of hypersensitivity in this study: Negative DPT.

Patients who could not meet criteria for a positive or negative diagnosis were considered inconclusive.

Rapid Drug Desensitization (RDD)

The tolerance induced by RDD is temporary; therefore, candidate patients received all following oxaliplatin treatments by means of RDD. Our group has previously validated an RDD protocol which is designed to last approximately 4 hours**[5,7].** Table 2 presents a practical example of an RCUH/RDD protocol designed for 1 of the study patients and shows information on protocol design.

We considered candidate patients for RDD those who met these inclusion criteria: (i) patients who had suffered symptoms compatible with immediate type I DHRs during the drug infusion; (ii) who had a first-choice indication, by their

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referring oncologist, to be treated with the culprit drug; (iii) who signed informed consents; and (iv) who showed either a high-risk assessment or a positive final diagnosis for oxaliplatin hypersensitivity.

Patient selection from this cohort for survival analysis

Cases: in order to maintain homogeneity, only patients with advanced colorectal cancer were included in this study, according to the following inclusion criteria:(i)confirmed diagnosis of advanced colorectal cancer with objective and measurable oncological disease stage IV AJCC Cancer Staging Manual**[22]**;(ii)ECOG performance status of 0-1**[23]**;(iii)life expectancy greater than 12 weeks;(iv)receiving oxaliplatin by means of RDD after suffering an DHR to oxaliplatin;(v)signed informed consents.

Controls: All controls were selected from patients who were receiving treatment with oxaliplatin by means of standard infusions at our institution during the same period of time the cases were being treated, and who met the following previous inclusion criteria: (i), (ii), (iii), and (v).

We selected a group of unequivocally non-hypersensitive control patients. Non-reactive controls were retrospectively selected from the Medical Oncology Department databases and selected by matching sex, right-sided primary tumor location, grade of histological differentiation, therapeutic line, and KRAS mutation. Additionally, we added to this group those patients from the Allergy Division cohort with a negative allergy workup (hypersensitivity ruled out by negative ST and negative DPT, and never subjected to RDD).

Given that some added controls (those added after a negative allergy workup) are arguably ´matched controls´, we used logistic regression to compare characteristics between controls and cases and ensure adequate matching.

Informed consent statement

This study was approved by the Ramon y Cajal University Hospital (RCUH) Ethics Committee, which validated informed consents that needed signing by patient, allergist, and referring oncologist.

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Endpoints

The **primary endpoint** of this study is overall survival (**OS**: time from the beginning of oxaliplatin treatment/RDD to death by any cause).

Secondary endpoint: Progression-free survival (**PFS**: time from the beginning of oxaliplatin treatment/RDD to disease progression or death by any cause).

Statistical analysis

Power calculation determined that at least 203 patients (patients plus controls) were needed to detect a clinically significant difference in survival between groups (HR=0.67), with a p-value of 0.05 and a power of 0.8. We set the ratio of 1:2 between cases and controls to achieve the total sample size with our selected 67 patients. Univariate Cox proportional hazards regression was performed for the survival analyses, and the multivariate Cox regression model was performed to assess prognostic variables. The potential prognostic variables that we selected were age, sex, primary tumour location, grade of differentiation, KRAS mutation, stage of the disease, primary tumour resection, surgery of metastatic disease, number of metastatic locations, therapeutic line, type of biologic treatment combined with chemotherapy, number of desensitization doses, best radiological response rate and the number of therapeutic lines received after de desensitization treatment. Survival analyses between groups were performed using Kaplan-Meier survival curves and a log-rank test. Analyses included all case patients who received at least one dose of oxaliplatin by means of RDD. All results with a p value of <0.05 were considered statistically significant. All analyses were carried out using the statistical package STATA version 13, College Station, TX.

In retrospective analyses, we further assessed if there was any association between tumor KRAS mutation status and oxaliplatin DHRs. Analyses included all case patients who received at least one dose of oxaliplatin by means of RDD.

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Results

Patient characteristics

During this 7-year period, 102 patients with advanced colorectal cancer (stage IV) were referred to our Desensitization Program after an oxaliplatin DHR.

In these 102 referred patients, median age was 63 years old (ranging from 21 to 85), and 53% (54/102) were men. In 18/102 (18%) patients oxaliplatin hypersensitivity was ruled out by means of a negative DPT, and could continue receiving standard administrations of oxaliplatin (no need for RDD).

After completing Allergy workup in these 102 patient, only 67 patients (67/102, 66%) received oxaliplatin by means of RDD (65 had a positive diagnosis of hypersensitivity and 2 were inconclusive, according to our criterion standard). These 67 patients qualified as cases.

In the group of 67 cases all initial reactions occurred within 1 hour of oxaliplatin administration, and all were consistent with immediate type I DHRs. We found no patients presenting with nonimmediate DHRs. Initial reaction was moderate or severe (grades 2 or 3) in 60%(40/67), including 5/40 patients presenting with anaphylactic shock and cardiovascular collapse. On the other hand, 40%(27/67) of patients suffered a mild initial reaction (grade 1). Before the initial DHR, cases received a median of 11 uneventful oxaliplatin sessions.

Characteristics of the 67 cases were very similar to those of the 102 referred patients: median age was 63 years old (however, ranging from 22 to 85) and 57%(38/67) were men. The most common chemotherapy scheme involved in 57/67 cases was FOLFOX (leucovorin/5-fluorouracil/oxaliplatin). Other schemes were 5/67 patients on TOMOX (raltritexed/oxaliplatin), one patient on XELOX (capecitabine/oxaliplatin), and four patients received other schemes. Location of primary disease was left-sided colorectal cancer in 75%(50/67) of cases, and 57%(38/67) had well differentiated histology.

Bevacizumab was administered in combination with oxaliplatin in 55%(37/67) of cases. KRAS mutation was present in 45%(30/67) of cases. A total of 66%(44/67) of patients had 2 or more objective radiological metastases, and

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only 10%(7/67) of them had not received surgical treatment for metastases.

Patient characteristics and their diagnostic flow chart are further described in table 1 and figures 1-2.

A total of 17/102(17%) referred patients changed to an alternative therapy or discontinued their treatments with oxaliplatin: 8/17 patients had positive ST, and 9/17 patients did not consent to DPT and/or RDD, despite negative ST and initial mild reaction.

Controls

The remaining 18/102(18%) patients showed a negative allergy workup (hypersensitivity ruled out by negative ST and negative DPT, and never subjected to RDD). These patients were added to the control group.

Additionally, 125 patients were selected as controls from the Oncology Division's database and matched to have similar baseline characteristics.

The total number of controls summed up 143 patients.

Rapid Drug Desensitization

A total of 337 RDD were performed in 67 patients. All RDD were succesful and all case patients could receive their desired oxaliplatin administrations by means of RDD. A total of 45%(30/67) of cases underwent RDD over 6 times. Moreover, 51%(34/67) of cases underwent RDD at least twice before any event (death or progression), and only 3 patients were subjected to RDD just once, before death or progression. The largest number of oxaliplatin administrations per patient was 25 administrations. Safety profile was very good and similar to previous studies**[5,7]**, with no breakthrough-reactions occurring in 95% of RDDs (320/337). A total of 17 breakthrough-reactions were observed, and most of them were mild (11/17); 4/17 were moderate, and only 2/17 classified as severe.

Survival analysis

The total number of patients included for the survival analysis was 210 (67 cases and 143 controls). The added controls are arguably 'matched controls',

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but we did not find any differences in any of the matched variables except for age. Median age for cases (n=67) was 63 (ranging from 22 to 85) and it was 70 for controls (n=143), which was found to be a statistically significant difference. See table 1.

At the time of this analysis, 52/67 patients(78%) had progressive disease and 42/67 patients(63%) were dead. The median overall survival (OS), defined as the time from the start of treatment to death from any cause or the time of the last followup, was 23.7 months (95%CI:15.3-30.9) for cases, while for controls it was 34.5 months (95%CI:21.7-55.5). Differences between groups were not statistically significant (log-rank p=0.1;HR1.42;95%CI:0.93-2.17;p=0.104). The results remained not significant after adjusting by age (log-rank p=0.1;HR1.5;95%CI:0.97-2.36;p=0.07). Progression-free survival (PFS) in the cohort of cases was 8.8 months (95%CI:7.9-12.8), whilst it was 13.04 (95%CI:9.43-12.8) for the controls; again there were no significant differences between both groups even after adjusting by age (log-rank p=0.1;HR1.05;95%CI:0.70-1.56;p=0.83). See Figure 3.

Some patients in both groups (cases and controls) might have underwent surgery in their first diagnosis, only becoming patients with advanced colorectal cancer (stage IV) in a later phase after a progression. These patients might be in need of chemotherapeutic treatment a long time after their first diagnosis. Thus, we also show the data for OS defined as the time from first cancer diagnosis to death from any cause or the time of the last follow-up. This OS for cases(n=67) was 61.6 months(95%CI:55.6-82.8); while for controls(n=143) was 80.6 months(95%CI:77.1-not reached). Differences between groups were not significant (log rank p=0.1,HR1.22;95%CI:0.74-2.00;p=0.431). See Figure 4.

There are limited therapeutic options for advanced colorrectal cancer, and they are administered consecutively when radiologic progression is observed. Thus, the "therapeutic line" refers to the running order of the administration of the different treatments**[3]**. Among the cases, 7 patients were treated postoperatively, 24 patients were treated with a first-line treatment, 10 patients with a second-line treatment, 12 patients with a third-line treatments and 14 patients with further therapeutic lines (see figure 5). Survival times are usually

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different depending on the therapeutic line, and this was also true for our patients (see figure 5). Therefore we analysed and compared the data of OS (defined as the time from the start of treatment to death from any cause or the time of the last follow-up) between cases and controls stratifying by therapeutic line in which RDD was performed, and we found not statistically significant differences between groups (see figure 6).

Identifying survival prognostic factors in cases

In the univariate analysis, we found the following prognostic factors indicating a worse survival: poor histological differentiation (HR4.1;95%CI1.9-8.6;p<0.001), stage IV at diagnosis (HR1.8;95%CI:1.1-2.9;p=0.02), number of metastatic locations (HR1.4;95%CI:1.1-1.7;p=0.001), therapeutic line in which RDD was performed (HR1.9;95%CI:1.6-2.4;p<0.001) and treatment with bevacizumab combinations (HR3.1;95%CI:1.5-6.5;p=0.002). In the Cox regression multivariate analysis including these factors and age, the presence of stage IV at the time of diagnosis and the administration of RDD in later lines of treatment were the only significant and independent factors indicating a worse survival in our patients. See table 3.

Additionally, there were no association between KRAS mutation and presenting with a DHR, nor between KRAS mutation and severity of DHRs.

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Discussion

Primary and secondary endpoints

According to our results, there are not statistically significant differences in oxaliplatin efficacy outcomes in our population between cases (oxaliplatin-hypersensitive patients receiving oxaliplatin by means of RDD) and controls (patients receiving standard oxaliplatin infusions). Both groups showed equally effective results in terms of overall survival (OS) analysis as well as in subanalysis for OS and progression-free survival (PFS).

We obtained similar survival outcomes and similar expected patterns (such as differences in survival rates depending on therapeutic line) for our cases to those of the cases of previous survival analysis**[24-26]**. For example, while our median OS for third-line patients was 14.8 months, the median OS for classic third-line trials such as CORRECT**[26]** was 6.4 months; and 7.1 months for RECOURSE**[25]**. Regarding first-line patients, we obtained a median OS of 30.7 months, which is similar to the findings in classic trials such as FIRE-3**[24]**, in which the median OS was 28.7 months in the FOLFIRI/cetuximab group and 25.0 months in the FOLFIRI/bevacizumab group.

These data show that RDD does not seem to affect oxaliplatin efficacy when compared to standard infusions; and, therefore, receiving oxaliplatin by means of RDD could be an effective therapeutic alternative for oxaliplatin-hypersensitive patients (in our RDD population, allowing for a median of 30.7 months of OS in first-line treatments). Moreover, oxaliplatin shows better survival rates when it is administered in first-line treatments, and this pattern is observed also when it is administered by means of RDD. Therefore, RDD should become a key therapeutic technique to be considered in oxaliplatin-hypersensitive patients, and it should also be available as a sensible option in first-line treatments, not only as a late alternative for further lines.

The role of DPT

Similar to our findings, although with a different drug, other authors**[14]** showed that "*efficacy of carboplatin was not reduced in allergic patients"* and that *"RDD protocols are as effective as regular infusions*". Unfortunately, further

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comparisons are difficult to make, especially since that study showed no data on DPT. This limitation is relevant because up to 32% of platin-reactive patients may be nonhypersensitive (negative DPT) and, therefore, can avoid RDD**[6]**. Thus, data on DPT need to be disclosed in order to obtain high quality results and comparisons between different populations. Interestingly, only 18% in the special population of this study showed a negative DPT (patients with advanced colorectal cancer might be exposed to larger number of oxaliplatin sessions and therefore have a higher risk of sensitization).

Previous publications**[5-16]** discuss the unique role of the Allergist for effectively and safely assessing patients with DHRs to chemotherapy. An adequate Allergy assessment helps reactive-patients receive their first-choice treatment; and, additionally avoids unnecessary RDDs. In this study 83% of patients could directly benefit from the assessment and go on with an oxaliplatin treatment (either after negative DPT or by means of RDD), which might have been otherwise discontinued. Implementation of DPT helped 18%(18/102) of the study population to go on with standard oxaliplatin infusions after ruling out hypersensitivity to oxaliplatin (negative DPT). Additionally, systematic expert assessment is key to identify those patients who are more vulnerable to the non-zero risk of anaphylaxis during RDD**[5]**.

Even if more studies are needed for different drugs, we believe RDD must be a therapeutic option available for all oncological patients who present with DHRs to their first-choice treatment. Our results show data that help highlighting some key features of RDD which have been previously addressed**[6-15]**: RDD is an efficacious, cost-effective, and safe therapeutic option even in patients who present with severe DHRs provided that patients have access to adequate facilities (rapidly available intensive care unit, dedicated Allergy Technical Areas with specific risk management procedures, physical presence of allergist at bedside, appropriate nurse:patient ratio, monitoring, crash cart, and so forth); and, provided that they are appropriately assessed by expert Allergists leading a multidisciplinary team of trained personnel (pharmacists, nurses, medical intensive care unit personnel, and so forth) in close collaboration with referring Oncologists**[5]**.

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Limitations

There are some limitations to this study, namely being a single center study and issues with the control group regarding power calculations and matching. The initial analysis was not powered for evaluating the subanalysis of OS in the different treatment lines, making the results of this subanalysis by line of treatment prone to false negative ('non-inferior') results. Additionally, given the differences in age, the comparator arm is not completely a group of 'matched' controls (18 controls added after a negative allergy workup) ; however, specific statistical corrections for this were applied where necessary.

Conclusions

This is the first reported survival study in oxaliplatin-hypersensitive patients undergoing RDD. Data were obtained from one of the largest reported series of oxaliplatin-RDDs in patients with advanced colorectal cancer, accounting for 337 procedures in 67 patients over a 7 year period. In order to avoid selection bias, the diagnosis of oxaliplatin hypersensitivity in this cohort was only confirmed after a strict workup including DPT. In the light of the resulting data, RDD does not seem to affect oxaliplatin efficacy based on survival rates when compared to standard infusions, even when we stratify by therapeutic line. Therefore, receiving oxaliplatin by means of RDD could be an effective therapeutic alternative for oxaliplatin-hypersensitive patients, and it should also be available as a sensible option in first-line treatments, not only as a late alternative for further lines.

CONFLICT OF INTEREST STATEMENT

There are no potential conflicts of interest for any of the authors regarding this article. There are no financial interests, and there have been not any provision of study materials by their manufacturer for free or at a discount from current rates.

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TABLES AND FIGURES

Table 1. Baseline characteristics of the study population and comparison by logistic regression between cases and controls.

Characteristics	Cases (n=67)	Controls (n=143)	*P* value
Age (y), mean (range)	63 (22-85)	70 (18-97)	<0.05
Male/Female (%)	38/29 (57/43)	89/54 (62/38)	0.29
Primary site of disease (%)			
Right side	16 (24)	37 (26)	0.705
Left side	50 (75)	104 (73)	
KRAS mutation (%)			
Wild type	28 (42)	36 (25)	0.269
Mutant	30 (45)	39 (27)	
Histology (%)			
Well differentiated	38 (57)	50 (35)	
Moderately differentiated	20 (30)	65 (45)	0.802
Poorly differentiated	4 (6)	7 (5)	

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Table 2. RCUH standard rapid drug desensitization protocol for a total dose of 200 mg of oxaliplatin meant to be infused in 2 hours at 125 ml/h.

Total dose	200 mg		Solution concentration		Total dose in each solution (mg)		Drug
Solution A	250 ml		0.016 mg/ml		4		Oxaliplatin
Solution B	250 ml		0.16 mg/ml		40		Oxaliplatin
Solution C	250 ml		0.8 mg/ml		200		Oxaliplatin
Step	Solution	Rate (ml/h)	Administered volume (ml)	Time (min)	Administered dose (mg)	Fold increase per step (mg/min)	Approximative cumulative dose infused (mg)
1	A	88	22	15	0.0	NA	0.0
2	A	100	25	15	0.4	NA	0.4
3	A	200	50	15	0.8	x2	1.2
4	A	400	100	15	1.6	x2	2.8
5	B	88	22	15	0.0	NA	2.8
6	B	100	25	15	4.0	x2.5	6.8
7	B	200	50	15	8.0	x2	14.8
8	B	400	100	15	16.0	x2	30.8
9	C	88	22	15	0.0	NA	30.8
10	C	125	211.5	101.52	169.2	x1.6	200.0
Total infusion time: 236.52 min (3.9 h).							
Premedications: Ideally they should comply with the manufacturer's instructions and institutional protocols for standard oxaliplatin infusion. We do not recommend additional premedications with steroids or antihistamines as a measure to prevent breakthrough reactions **[5,6,12]**, however tailored premedication may be added (mainly montelukast and acetilsalicylic acid) depending on personalised physician decision making **[5-12]**.							
Total dose calculation and discarded volume: Not all the volume in solutions A, B, or C is infused. We start the protocol with solution A containing a 1/50 dilution, then solution B with a 1/5 dilution, and we end with a final solution C containing a full concentration of the culprit drug. Total dose to be infused during solution C is calculated by subtracting the cumulative dose administered in steps 1-8 from the total desired dose.							
Adjustments to the volume of the bags: The standard volume in the solution bags for the RCUH RDD protocol is 250 ml. In some cases, bag volume might need adjustment depending on manufacturer´s instructions.							
Additional bags for high risk patients: Whenever needed in high risk patients, additional solutions with lower concentrations than solution A may be added previous to solution A to ensure a more cautious starting dose, and whenever possible as determined on the basis of an endpoint titration according to local protocols (in case of positive skin tests).							
Flushing steps: Each solution uses an individual infusion line previously primed with 22 ml of the dilutor substance. Steps 1, 5 and 9 are considered “line flushing steps” (in which 22 ml of the dilutor substance are administered).							
Adjustments to final infusion rate: Step 10 may be adapted to the desired final infusion rate according to the standard regimes indicated by the referred oncologist (additional steps may be added in order to reach higher infusion rates while maintaining a maximum dose increasing by 2-fold to 2.5-fold with each step).							
Avoiding human errors: Infusion pumps with automatic multi-step infusion options (Alaris® SE double channel) were used to avoid human errors associated with manually changing infusion rates every 15 minutes. We used 22 ml infusion systems for these pumps (Alaris® SE I pump smartsite infusion set).							

Legend: RCUH, Ramon y Cajal University Hospital; NA, not applicable

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Table 3. Cox regression analysis including age and the prognostic factors identified in the univariate analysis.

	HR	***p***	***95%CI***	
Cases	2.86e+14	1.000	0	.
Age	1.01	0.715	0.97	1.04
Poorly differentiated	2.84	0.152	0.68	11.93
Stage IV at diagnosis	3.56	0.01	1.35	9.41
Number of metastatic locations	0.74	0.166	0.48	1.13
Line in which RDD is performed	2.03	<0.001	1.51	2.73
Bevacizumab treatment	2.13	0.092	0.88	5.15

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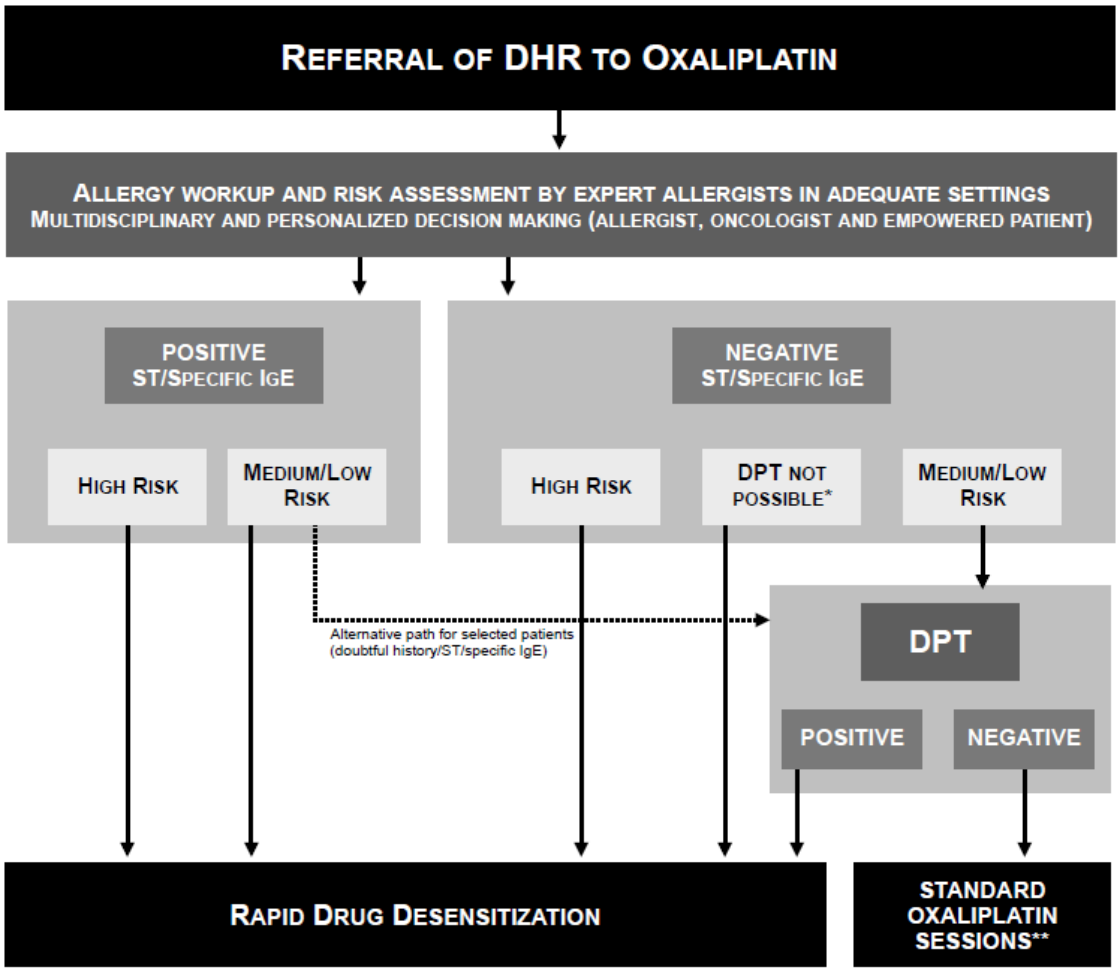
Figure 1. Flow Chart for systematic Allergy workup of referred DHRs to oxaliplatin in the RCUH Drug Desensitization Program.



Legend: DHRs, drug hypersensitivity reactions; IgE, immunoglobuline E; RDD, rapid drug desensitization; DPT, drug provocation test; ST, skin testing.

* DPT not possible (e.g. inadequate installations, insufficient personnel, patient does not consent to DPT, etc.).

** Platin-reactive patients receiving standard sessions after negative DPTs might be in need of tailored follow up including preventive screening ST, as 'positive converters' have been described **[6].**

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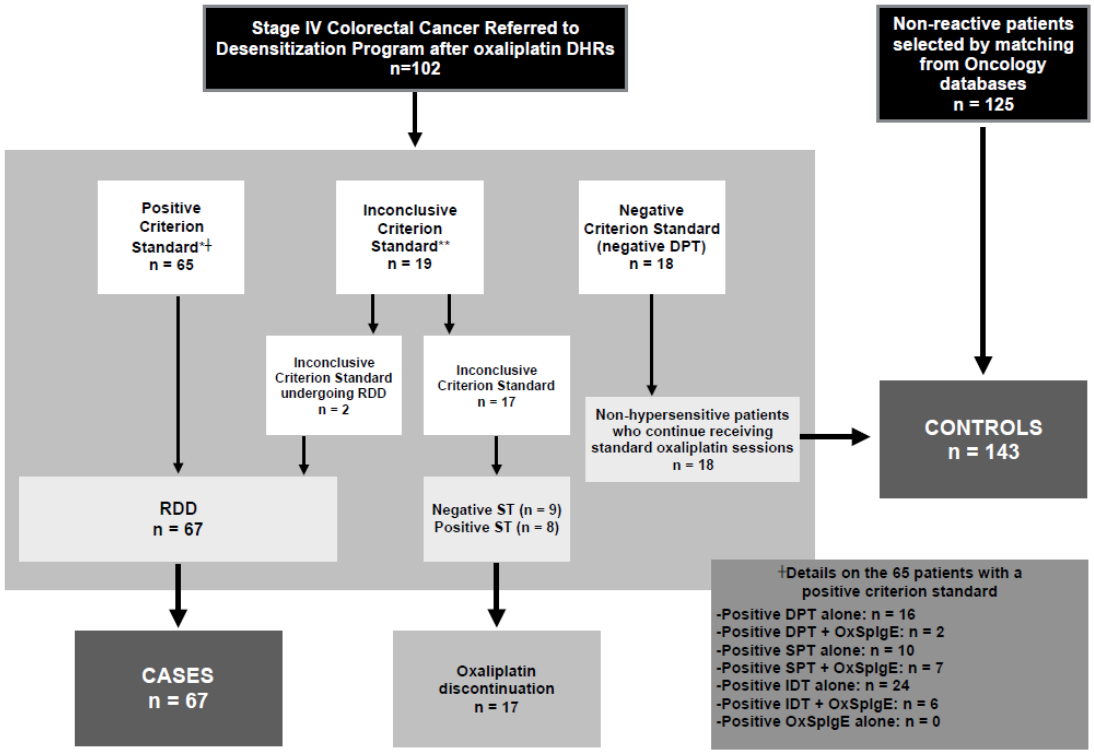
Figure 2. Diagnostic flow chart and group assignment for the study population.



Legend: DHR, drug hypersensitivity reaction; IgE, immunoglobuline E; RDD, rapid drug desensitization; DPT, drug provocation testing; SPT, skin prick testing; IDT, intradermal testing; OxSpIgE, oxaliplatin-specific IgE.

* Positive Gold Standard (unequivocal clinical history and positive skin testing and/or positive specific IgE and/or positive DPT).

** Inconclusive Gold Standard (patients who could not meet criteria for a positive or negative diagnosis). Some patients might be inconclusive because they abandon oxaliplatin treatment after the initial DHR (for different reasons, namely end of programmed treatment, do not consent, change to alternative therapy, etc.), and so further study is impossible.

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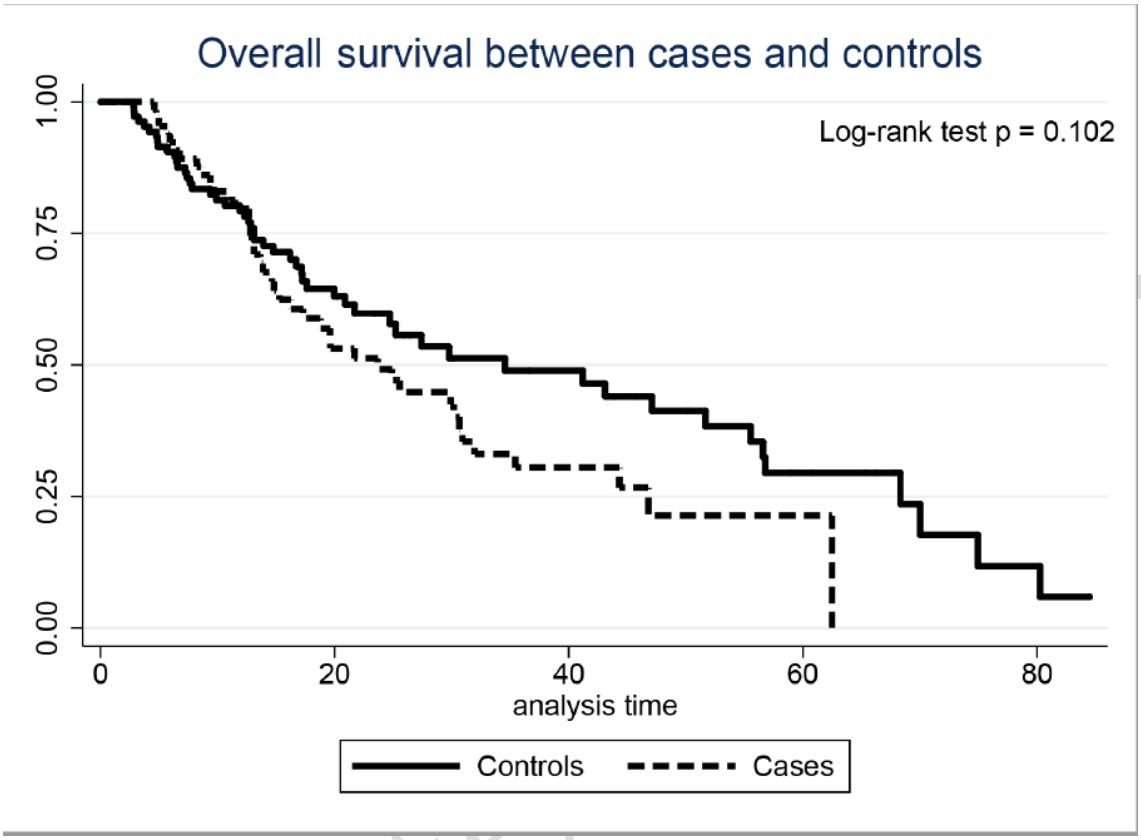
Figure 3 Curves for overall survival of 67 cases (RDD) and 143 controls (not RDD), defined as the time from the start of treatment to death from any cause or the time of the last follow-up.



Legend: RDD, rapid drug desensitization. Median overall survival time of cases was 23.7 months (95%CI 15.3 - 30.9); while for controls was 34.5 months (95%CI 21.7 - 55.5). After Log-rank curve comparison between cases (n=67) and controls (n=143), there were no significant differences between both groups (HR1.42;95%CI:0.93-2.17;p=0.104).

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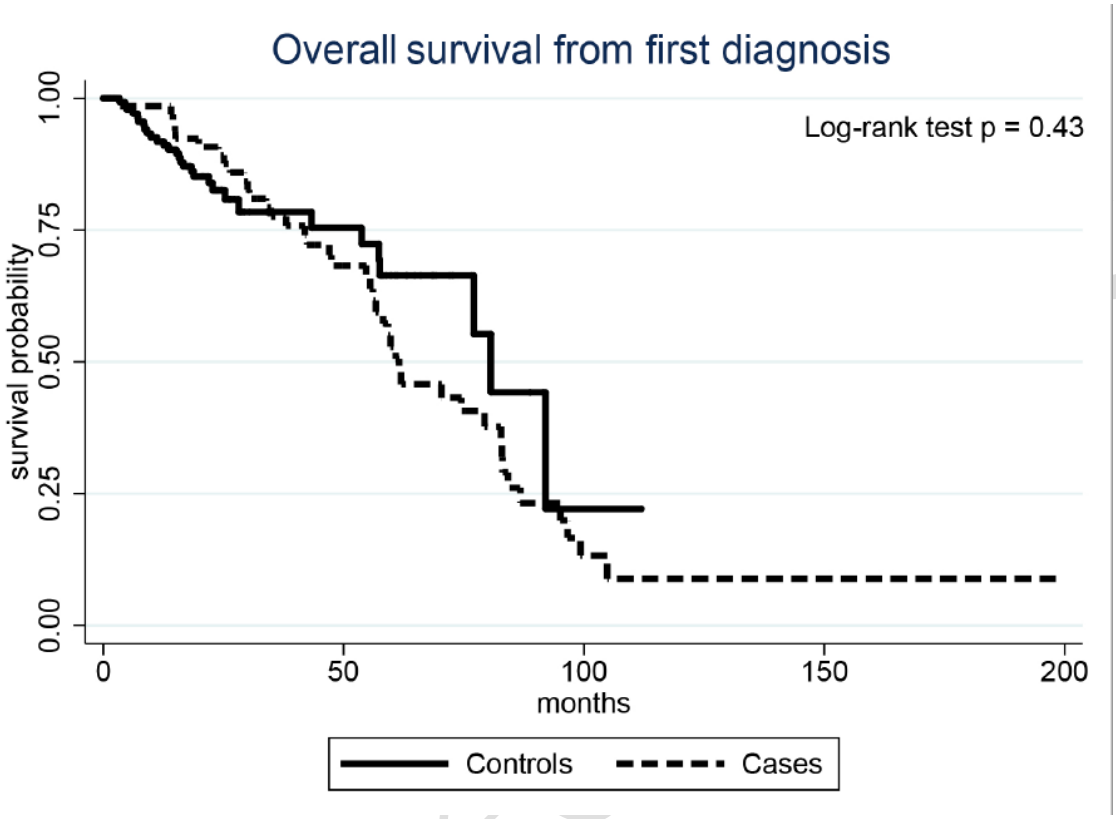
Figure 4 Curves for overall survival of 67 cases (RDD) and 143 controls (not RDD), defined as the time from cancer diagnosis to death from any cause or the time of the last follow-up.



Legend: RDD, rapid drug desensitization. Median overall survival time of cases was 61.6 months (95%CI 55.6 - 82.8); while for controls was 80.6 months (95%CI 77.1 - not reached). After Log-rank curve comparison between cases and controls, there were no significant differences between both groups (HR1.22;95%CI:0.74-2.00;p=0.431).

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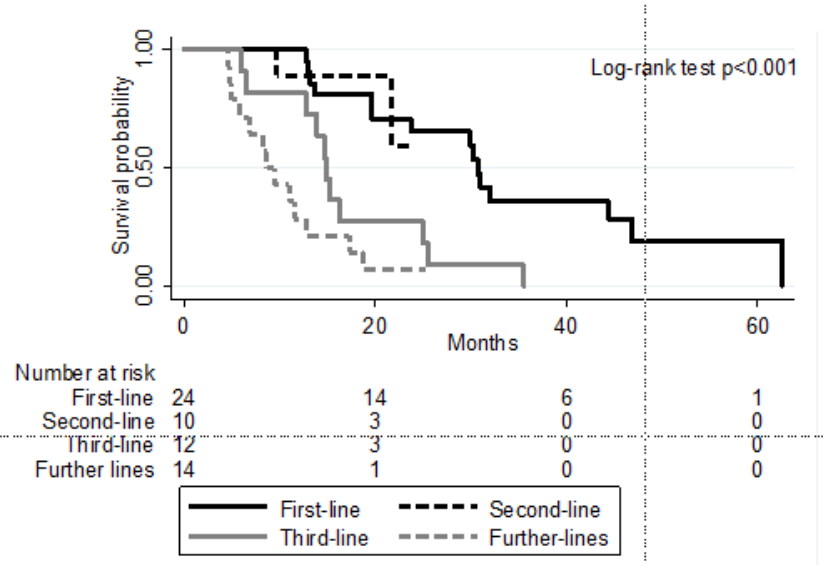
Figure 5. Curves for overall survival (defined as the time from the start of treatment to death from any cause or the time of the last follow-up) after stratification by line of treatment in the final 67 patients selected as cases (oxaliplatin hypersensitive patients undergoing Rapid Drug Desensitization).



Line of treatment	Patients (n)	Median (months)	95 % Confidence interval	
Adjuvant	7	*not achieved*	*not achieved*	*not achieved*
First-line	24	30.65298	19.6468	46.7844
Second-line	10	*not achieved*	9.69199	*not achieved*
Third-line	12	14.81725	6.43942	24.9035
Further lines	14	8.574948	4.99384	12.6817
All lines	67	23.68789	15.2772	30.9158

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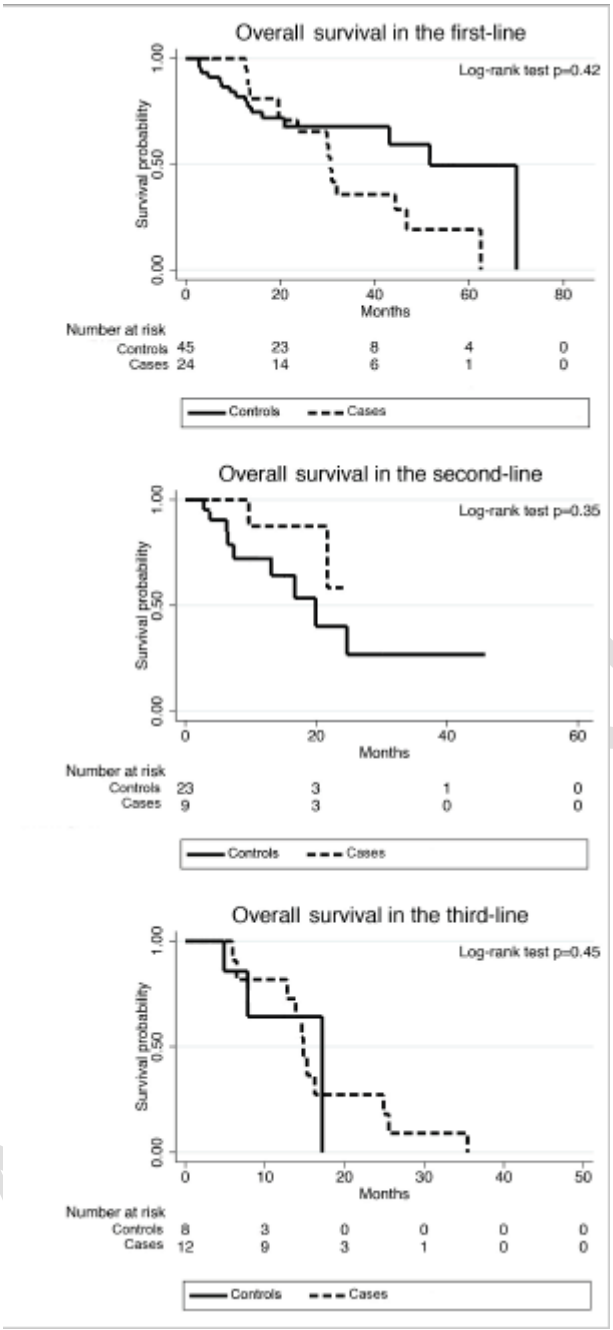
Figure 6. Curves for overall survival (defined as the time from the start of treatment to death from any cause or the time of the last follow-up) after stratifications by line of treatment and comparing cases with controls.



Legend: DHR, drug hypersensitivity reaction; RDD, rapid drug desensitization; DPT, drug provocation test.

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