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Phase I Dose Escalation Study of Concurrent Palliative Radiation Therapy with Sorafenib in Three Anatomical Cohorts (Thorax, Abdomen, Pelvis): the TAP Study

Louise Murray[1,2], Joseph Longo[2,3], Jonathan Wan[1,2,6], Caroline Chung[1,2], Lisa Wang[4], Laura Dawson[1,2], Michael Milosevic[1,2], Amit Oza[5], Anthony Brade[1,2,6]

1. Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada
2. Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, 610 University Avenue, Toronto, Ontario, Canada
3. Department of Medical Biophysics, University of Toronto, Ontario, Canada
4. Department of Biostatistics, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada
5. Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada
6. Present address: Department of Radiation Oncology, Mississauga Halton Central West Regional Cancer Program, 2200 Eglinton Avenue West, Mississauga, Ontario, Canada

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Corresponding author:

Dr Anthony Brade,
Department of Radiation Oncology,
Mississauga Halton Central West Regional Cancer Program,
200 Eglinton Avenue West,
Mississauga,
Ontario L5M 2N1
E-mail: Anthony.Brade@trilliumhealthpartners.ca
Telephone: 905 813 1100 ext 4803
Fax: 905 813 3962

Abstract

Background and Purpose: To evaluate the tolerability and maximum tolerated dose (MTD) of sorafenib administered concurrently with palliative radiotherapy.

Material and Methods: In patients with incurable cancer, sorafenib was escalated independently in three cohorts based on irradiation site: thorax, abdomen or pelvis. Sorafenib was administered days 1-28 and radiotherapy (30Gy in 10 fractions) was delivered days 8-12 and 15-19. Dose-limiting toxicities (DLT) were acute grade 3+ toxicities attributable to radiotherapy.

Results: For the thorax, abdomen and pelvis cohorts, 14, 16 and 4 patients were recruited, and Dose Levels 3, 3 and 2 were reached, respectively. Sorafenib-related systemic toxicity led to significant sorafenib interruption in 10 patients. There were 3 DLTs in total, one per cohort: grade 3 oesophagitis (thoracic), transaminase elevation (abdominal) and grade 5 bowel perforation (pelvic; patient with tumour invading bowel). Grade 2 radiation dermatitis developed in 12 patients. The trial was terminated early as slow accrual and sorafenib-related systemic toxicity prevented efficient evaluation of RT-related DLTs.

Conclusions: The MTD of sorafenib when used with 30Gy in 10 fractions was not established due to sorafenib-related systemic toxicity. Severe radiotherapy-related toxicities were also observed. These events suggest this concurrent combination does not warrant further study.

Introduction

Palliative radiotherapy (RT) is an established treatment for patients with symptomatic, incurable cancer[1-5]. Side effects are typically local to the irradiated area, and so vary with anatomical site.

Sorafenib is a multi-targeted tyrosine kinase inhibitor with activity against Vascular Endothelial Growth Factor, Platelet-Derived Growth Factor, Raf and Kit[6,7]. Clinical activity is reported in renal[8], hepatocellular (HCC)[9] and differentiated thyroid cancers[10].

At the time of trial set up pre-clinical studies had demonstrated that the use of a range of anti-angiogenic agents in combination with RT, could enhance the response to radiation[11-18]. This was demonstrated in multiple cell lines, including, for example, head and neck[18], lung[13,18] and colorectal cancers[11,12]. This raised interest in the potential clinical benefit of combining agents such as sorafenib concurrently with RT. When designing this trial, no clinical evidence existed regarding sorafenib in combination with RT. There was, however, an appreciation that combining two agents that both impact on vasculature might not be without risk and that existing clinical data regarding bevacizumab with RT, had demonstrated marked toxicities [19-21].

This study aimed to evaluate the tolerability and maximum tolerated dose (MTD) of sorafenib when used in conjunction with palliative RT. Given the factors discussed above, this trial was designed to evaluate the combination in a phase I dose-escalation setting and using an established, minimally-toxic palliative RT regimen. As such it was hypothesized that any RT-drug interactions could be identified in a relatively safe manner compared to using radical RT dose-ranges. In addition, as RT toxicities are generally local and related to the interplay of dose-volume effects on irradiated tissues, patients were enrolled into, and sorafenb dose escalated independently within, three cohorts: thorax, abdomen and pelvis, depending on irradiated area, in an effort to detect variation in tolerability of the treatment combination between different anatomic locations.

Material and Methods

This single institution, open-label, phase I trial was approved by the institutional Research Ethics Board.

Patients

Patients had incurable cancer, with a measurable soft tissue lesion in the thorax, abdomen or pelvis. Patients were ≥18 years old with prognosis ≥3 months, Eastern Cooperative Oncology Group performance status 0-1 and adequate organ and marrow function (Supplementary Material). Exclusion criteria included overlap of planned radiation with previously irradiated volumes, inability to meet RT dose constraints, prior sorafenib, uncontrolled brain metastases and anticancer therapy within 4 weeks of sorafenib. Given potential sorafenib toxicities, patients with poorly controlled hypertension, bleeding disorders and cardiac dysfunction were excluded. Bone-only lesions were excluded, as these were considered non-measurable.

Sorafenib

Patients received sorafenib orally on days 1-28, starting one week pre-RT. Radiotherapy was delivered concurrently during weeks two and three (days 8-12, 15-19). For each anatomic cohort, dose escalation proceeded independently according to a standard 3+3 protocol. Table 1 outlines planned dose levels.

Patients were removed from the trial if there was delay or discontinuation of sorafenib for ≥14 days due to systemic sorafenib-related toxicity. The Principal Investigator could also replace patients requiring substantial sorafenib dose reductions based on individual review. Removed patients were replaced at the

same Dose Level. Patients were considered to have completed sorafenib if ≥50% of the planned dose was taken without delay or discontinuation lasting ≥14 days.

Radiotherapy

Conformal RT was CT-planned. Intravenous or oral contrast was permitted. Radiotherapy was delivered to gross disease (+/- clinical target volume (CTV) at physician's discretion) and ≥5mm planning target volume (PTV) for set-up variation and organ motion. The prescription was 30Gy in 10 fractions, once daily, days 8-12 and 15-19. Treatment was planned using ≥2 high-energy (≥4MV) photon beams. It was mandated that the gross tumour volume (GTV) and PTV received ≥95% and ≥92% of the prescribed dose, respectively. Simple field arrangements were encouraged, although intensity-modulated radiotherapy (IMRT) was permitted, if necessary, to meet constraints (Table 2). Verification was performed using orthogonal x-rays or cone beam CT on RT day 1, and as indicated thereafter.

Toxicity Assessment

Toxicities were assessed using Clinical Trials Criteria for Adverse Events (CTCAE) version 3.0. Dose-limiting toxicities (DLT) were defined as acute (during combination therapy or within 8 weeks post-RT) grade 3+ toxicities attributable to RT (i.e. toxicities local to the irradiated field, potentially exacerbated by sorafenib). Expected sorafenib-related systemic toxicities were not DLT (e.g hypertension, hand-foot syndrome (HFS), asymptomatic electrolyte abnormalities, grade 3 cytopaenia and diarrhoea (unless the RT field included bowel and symptoms uncontrollable)).

Patient follow-up and evaluation

During weeks 1-4, patients were reviewed weekly by Medical and Radiation Oncologists with sorafenib dose adjustments as described in Supplementary Material. Patients were reviewed two-weekly during weeks 5-12, two-monthly for the next 6 months, then quarterly. Imaging was performed 8 weeks post-RT, then prior to each visit. If response was observed in the target lesion, a confirmatory scan was performed 4-6 weeks later. Local (i.e. in-field) response was assessed using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Out-of-field responses were not used for response evaluation.

Statistics

Primary endpoints were to evaluate the tolerability and MTD of sorafenib when used concurrently with palliative RT by anatomic region (thorax, abdomen, pelvis). Best local response was recorded as a secondary endpoint in patients who completed sorafenib. Progression free survival (PFS) and overall survival (OS) were calculated from date of first sorafenib using Kaplan-Meier methodology and SAS version12.1 (SAS Institute Inc, NC).

Results

From May 2007 to October 2010, 34 patients were registered (Table 3). In the thorax, abdomen and pelvis cohorts, 14, 16 and 4 patients were recruited and Dose Levels 3, 3 and 2 were reached, respectively. All but 2 patients completed RT. One did not start RT as target liver volumes were too large. This patient was removed and replaced. The other patient completed 9/10 fractions but declined the final fraction due to sorafenib-related HFS, limiting her ability to attend. 31 patients received 2-4-field treatments, and 2 received 5-7-field IMRT.

Systemic sorafenib toxicities (grade 2/3 HFS, diarrhoea and hypertension, i.e. toxicities *un*related to RT) resulted in early drug discontinuation in 10 patients: 2, 5 and 3 patients at Dose Levels 1, 2 and 3, respectively (Table 4). Of these 10 patients, 8 omitted ≥50% of the planned sorafenib dose. Overall, 5 patients were replaced due to drug-related toxicity prior to termination of the study (Table 4).

Of the 23 patients considered to have completed the 28-day course of sorafenib (i.e. ≥50% of planned dose received, no breaks lasting ≥14 days), 16 had no dose modifications (7/7, 6/9 and 3/7 patients at Dose Levels 1, 2 and 3, respectively) and 4 had minor modifications (i.e. >90% of planned dose completed with modifications due to mild transient systemic toxicities (n=2), intercurrent illness (n=1) or patient error (n=1)). Three patients at Dose Level 3 who completed sorafenib required substantial dose modifications due to sorafenib-related toxicities (grade 3 thrombocytopaenia, grade 3 rash and grade 2 HFS; 36-50% sorafenib omitted). Six of 10 patients treated at Dose Level 3 required drug discontinuation or modification due to systemic toxicity.

In total, 33/34 patients were evaluable for DLT (i.e. grade 3+ RT-related toxicities). The remaining patient did not start RT (above). DLTs were observed in all cohorts (Tables 4 and 5).

In the thoracic cohort, Dose Level 2 was expanded from 3 to 6 patients due to grade 3 esophagitis in a patient who received 4-field mediastinal RT for metastatic chondrosarcoma. This patient received the highest V25 (percent oesophagus receiving ≥25Gy) in the series (39%). Oesophageal maximum and mean doses were 32Gy and 16Gy, respectively. Oesophagitis began in week 3, requiring hospitalisation on Day 22 for supportive measures for 6 days.

In the abdominal cohort, Dose Level 3 was expanded due to grade 3 transaminitis in a patient receiving RT for 2 liver metastases, delivered as 2 parallel-opposed pairs to separate liver regions. Maximum and mean liver (minus GTV) doses were 31Gy and 9Gy, respectively. The liver volume receiving <1Gy was at the protocol limit (35%). The asymptomatic transaminitis began 6

days after completing sorafenib. At baseline, ALT was normal and AST was one unit above ULN. Transaminases resolved to baseline within 2 weeks.

In the pelvic cohort, one patient treated at Dose Level 2 developed small bowel perforation at the site of tumour invasion, resulting in death. The patient had peritoneal carcinosarcoma with large-volume disease. Sorafenib was discontinued on Day 19 due to grade 3 diarrhoea. The patient was admitted on Day 24 with bowel obstruction leading to perforation, sepsis and death on Day 29. The maximum and mean small bowel doses received were 31Gy (104%) and 10Gy, respectively and the small bowel volume receiving ≥30Gy was 4%, well within the protocol-specified limit (33%). A protocol amendment excluded future patients with tumour-involved bowel or considered high-risk for fistula.

No other high-grade, RT-related toxicities occurred.

Acute increased dermatitis within the RT field was observed in 22 patients: 10 grade 1 and 12 grade 2 (Figure 1). Grade 2 radiation dermatitis occurred in 1, 7 and 4 patients at Dose Levels 1, 2 and 3, respectively. This included patients who failed to complete 4 weeks of sorafenib. Of patients who received ≥4-field radiation, only 1/11 had radiation dermatitis >grade 1 (9.1%), while 11/22 (50%) who received 2/3-field RT developed grade 2 radiation dermatitis (Fisher's Exact p=0.027). Of 9 patients who received Dose Level 1, one (11%) experienced radiation dermatitis >grade 1, while 11/24 (45.8%) who received Dose Level 2/3 experienced grade 2 radiation dermatitis (p=0.107).

The trial was terminated as slow accrual, together with excessive sorafenib-related systemic toxicity resulting in frequent dose reductions and discontinuations at 400mg bid (required in 60%), meant that efficient evaluation of toxicity related to combined radiation and sorafenib at this dose was infeasible. The observed frequency of significant sorafenib dose modifications due to systemic sorafenib toxicities, particularly at higher sorafenib doses, exceeded that anticipated during the design and budgeting of the study. A revised projection effectively doubled of the number of patients needed to

complete the study to account for drop out due to sorafenib systemic toxicity, exceeding the approved budget and led the study sponsor to request the study be terminated. The MTD was therefore not determined for any cohort.

In total, 23 patients were evaluable for best local response (Table 4). The remaining 11 were inevaluable because of: failure to complete sorafenib due to systemic toxicities (i.e. ≤50% planned dose completed and discontinuation/delay ≥14 days, n=8), CT follow-up in patient originally imaged using MRI (prohibited by RECIST, n=1), failure to start RT (n=1) and death on study (n=1). Results are summarized in Table 4. No complete responses were observed.

One patient on sorafenib 400mg bid in the abdominal cohort with metastatic large cell pancreatic neuroendocrine cancer with widespread lymphadenopathy had radiological response in the irradiated para-aortic field and elsewhere. Sorafenib was continued for five months, at which point out-of-field progression occurred. Control continued in the irradiated region for 3 years.

Median PFS and OS for all patients were 5.9 (95%CI: 4.7-7.4) and 10.8 (95% CI: 6.4-17.6) months, respectively. Estimated 12-month PFS and OS were 22% and 44% respectively.

Discussion

This study aimed to determine the tolerability and MTD of sorafenib used in conjunction with 30Gy in 10-fraction palliative RT. Dose-limiting toxicities were defined as acute grade 3+ toxicities attributable to RT, (i.e. not expected sorafenib-related systemic toxicities). Systemic sorafenib toxicities did interfere

9

with accrual however, as patients rendered ineligible due to significant dose reductions and delays for this reason were required to be replaced on study. This increased the number of patients required to complete the study beyond the approved budget leading to early study termination. Relevant to the primary outcome, however, three patients experienced DLTs (i.e. severe RT-related toxicities).

At the time of trial design, there was no published clinical data regarding sorafenib delivered concurrently with RT. Since completion of this study, however, sorafenib with RT has been investigated in early phase trials in HCC[22-24], high grade glioma (HGG)[25,26], soft tissue sarcoma (STS)[27], and cervical[28], pancreatic[29] and rectal[30] carcinomas. As in this study, systemic sorafenib-related toxicities commonly result in drug discontinuation or modification. For example, in a phase II trial in HCC administering sorafenib 400mg bid with 40-60Gy (≤2.5Gy fractions), 40% of patients required sorafenib discontinuation or modification for HFS or diarrhoea[22]. Similarly, in a phase I study of sorafenib, temozolomide and RT in HGG, 55% discontinued sorafenib, 400mg bid, largely due to sorafenib-related toxicities[26].

Where RT-related toxicities in response to RT-sorafenib have been assessed, substantial toxicity has occurred. In the above-mentioned trial in HCC, 4 patients (10%) developed grade 3 hepatic toxicity during concurrent RT-sorafenib and 9 (25%) developed grade 3+ toxicity during sequential sorafenib monotherapy; 6 of these 9 high-grade events, including 3 deaths, occurred without intrahepatic tumour progression[22]. Sorafenib and 6-fraction stereotactic body radiotherapy (SBRT; 30-51Gy) was also evaluated in HCC in a phase I trial and again, high-grade toxicity occurred with 9, 2 and 1 episode(s) of grade 3, 4 (liver enzyme changes and bowel obstruction) and 5 (gastrointestinal bleed/ HCC rupture) toxicity respectively, all at least possibly attributable to RT[23]. In the current study, we observed 2 grade 3 and 1 grade 5 DLTs, illustrating that severe toxicity can occur, even with low-dose RT.

The DLTs in this study included grade 3 transaminitis and oesophagitis, and grade 5 bowel perforation. Hepatic toxicities have been previously observed with higher liver RT doses and sorafenib in HCC, as above[22,23]. In this current study, however, grade 3 transaminitis occurred in a patient with liver metastases and essentially normal liver function, illustrating that patients with intact liver function are also at risk of severe hepatic toxicity. In a related institutional study evaluating sorafenib with whole liver RT or 6-fraction SBRT in patients with good liver function and liver metastases, severe hepatic toxicity also occurred[31]. For the case of grade 3 oesophagitis, this patient received the highest oesophageal V25 in the series. Following the single case of grade 5 perforation of tumour-involved bowel, the protocol was modified to exclude patients with tumour invading bowel or at high-risk of fistula. Since this trial, luminal toxicities and fistulation have been reported elsewhere following sorafenib with RT, including in the absence of tumour. These include grade 3-5 colonic perforations, intestinal bleeds, obstruction and gastric ulcers and vesico-vaginal fistulation in a patient with advanced cervical cancer[23,28,32,33]. Luminal toxicities and fistula formation are therefore realistic concerns.

An unexpectedly high frequency and severity of radiation dermatitis was observed, including grade 2 reactions in 36%, especially in those receiving 2-3-field RT. Interestingly, most subsequent sorafenib-RT trials do not report radiation dermatitis. Only the study investigating sorafenib-RT in extremity STS reported mild/moderate radiation dermatitis in all patients[27]. One case study also reported grade 2 radiation dermatitis in a patient receiving sorafenib 400mg bid concurrent with 2-field palliative thigh RT (36Gy, 12 fractions) for intramuscular metastatic deposits[34]. The lack of reported radiation dermatitis could be because multi-beam RT reduces skin dose compared to simpler arrangements. The dose threshold for this effect may be quite low however, as evidenced by the reaction within each portal in a patient (Figure 1) treated with a wedged-pair (~9Gy isodose at skin surface). The case of severe radiation-induced oesophagitis suggests a similar process may affect mucosal reactions.

Although not the primary aim, best local responses were also assessed. Partial responses and stabilisation were observed in 26% and 48% respectively, within the 13-55% and 17-73% reported in other early phase sorafenib-RT trials[22,24-26,29]. In the setting of palliative RT, symptomatic changes are often used to assess response rather than radiological changes. Historically, palliative RT results in symptomatic improvements in 45-100% of patients with soft tissue disease[1-5]. If it is assumed that symptomatic improvement corresponds to response or stabilisation, then the radiological responses observed here are not substantially better than the symptomatic responses achieved with palliative RT alone.

This current study evaluated sorafenib and palliative RT, whereas existing published series employ higher RT doses. Acknowledging the limited patient numbers and that the primary objective (defining MTD of sorafenib in each anatomic cohort) was not met, this study forms the largest series investigating palliative RT and concurrent sorafenib. A hypothesis of this study design was that it could facilitate the identification of drug-radiation interactions using palliative RT and this is supported, based on congruence of observed toxicities with those documented in other studies using higher dose RT. In addition, the observation that sorafenib delivered concurrently with RT can result in severe RT-related toxicities is highly relevant to day-to-day practice. This study provides evidence that, for patients requiring palliative RT while on sorafenib, the decision to continue or interrupt sorafenib during RT, potentially compromising systemic control, requires careful consideration.

A further limitation, and potential criticism, of the trial is that sorafneib was administered in disease sites for which there is a lack of molecular/clinical rationale for its use. However, pre-clinical data at the time of study design had demonstrated that radiotherapy resulted in the production of pro-angiogenic cytokines in several tumour cell types and that blockage of these with anti-angiogenic agents enhanced RT effect[35,36(review)] and anti-angiogenic agents had been shown to reduce hypoxia by improving vasculature efficiency in a variety of experimental tumour cell models[36-38]. In addition, the role of

sorafenib in the clinical armamentarium was not completely defined. Therefore, it was hypothesized that this drug might enhance RT efficacy and that evaluation of the safety of the combination in a broad range of tumour types would be of clinical interest. As a phase 1 trial however, the primary endpoint was toxicity and the trial was modelled after a standard phase 1 systemic therapy study, enrolling patients who have exhausted standard therapies, and also met eligibility criterion for potential benefit from radiotherapy. The design was further adapted to account for the local nature of RT toxicity through incorporation of anatomically-based, independently accruing cohorts.

The results demonstrated that there are difficulties in successfully administering palliative RT with concurrent sorafenib, both in terms of sorafenib-related systemic toxicities and severe RT-related toxicities. While disease response or stabilisation may occur, the combination does not appear superior to palliative RT alone. If the combination were to be evaluated further, this may be more feasible using multi-beam arrangements and lower dose sorafenib. Based on this trial however, in a palliative setting, where improving quality of life guides treatment decision-making, further investigation of concurrent full dose sorafenib and simple low dose RT is unwarranted. In addition, this trial design may be useful in assessing the risk-benefit ratio of combining other molecularly targeted therapies with palliative radiotherapy, addressing an increasingly common clinical scenario, while simultaneously providing valuable information regarding drug-radiotherapy interaction relevant to the radical treatment space.

Conflict of interest statement

Figure Legends

Figure 1. Patient with grade 2 radiation dermatitis who received 30Gy in 10 fractions as an oblique parallel-opposed pair concurrent with sorafenib (200 mg bid) to a metastatic para-renal mass. Well-demarcated area of hyperpigmentation and dry desquamation noted after 1 fraction of radiotherapy.

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