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Evaluating the benefits of transitioning from intravenous to subcutaneous Rituximab for Alberta cancer patients

by Cherie C. Severson

ABSTRACT

A novel approach to treating cancer in the settings of Non-Hodgkin’s Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL) is the use of a subcutaneous (SC) injection of Rituximab (in addition to standard combination chemotherapy). Alberta cancer patients can safely benefit from the administration of subcutaneous Rituximab in numerous ways while still ensuring efficacy and optimal treatment for their cancer. Review of the American literature revealed several studies indicating the benefits of SC Rituximab. The Spark Thera trial revealed pharmacokinetic results of Rituximab concentrations in NHL patients who were administered a fixed dose of 1,400 mg (625 mg/m²) SC achieved non-inferior Ctrough and AUC levels compared to those patients administered the standard IV dose of 375 mg/m². The SABRINA study results reveal an ORR 54% (IV+ chemo) versus 57% (SC + chemo); CR 19% versus 29% respectively and PR 35% versus 37% respectively with comparable safety profiles. The Sawyer B02341 Phase 1b study shows non-inferior pharmacokinetics and comparable safety profiles using a fixed dose of 1,600 mg of Rituximab SC compared to Rituximab 500 mg/m² IV in patients with CLL receiving combination (FC) chemotherapy. Further American studies report relative reductions in mean chair time, reduced pharmacy preparation time and increased ability to improve the number of other patients that can be treated increasing a facility’s overall efficiency by administering SC Rituximab. Given another option, patients can spend less time in a cancer facility freeing up bed and chair space for other patients needing treatment (De Cock et al., 2013a & 2013b).

Key words: subcutaneous Rituximab, intravenous Rituximab, cost analysis, drug access

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THE NOVEL APPROACH

Rituximab is a monoclonal antibody that targets the CD20+ B cell and is commonly used to treat hematologic disorders such as Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin’s Lymphoma (NHL) (Mao, Brovarney, Dabbagh, Birnbock, Richter, & Del Nagro, 2013). In Alberta, Rituximab is approved to be administered via intravenous route only (Alberta Health Services (AHS, 2013). It is well documented there is greater potential for a risk of hypersensitivity associated with the use of this drug intravenously (Mao et al., 2013). Due to the risk of hypersensitivity, prophylactic medications are administered prior to chemotherapy (Biogen Idec and Genentech, 2006). This approach, however, increases the patient’s time spent in the treatment area, as well as the preparation time the nurse must take to treat the patient. The first infusion of Rituximab is administered over four to six hours (Biogen Idec and Genentech, 2006). If the initial infusion is well tolerated, subsequent infusions can be administered via rapid infusion over 90 minutes (Biogen Idec and Genentech, 2006). Overall, this is a lengthy treatment. Given another option, patients can spend less time in a treatment area freeing up bed and chair space for other patients needing treatment (De Cock, Kritiou, Tao, Weisner, Waterboer, & Carella, 2013). In addition, the preparation time and cost of supplies utilized by health care professionals (both nurses and pharmacists) could be reduced and the overall efficiency of a treatment area can be improved (De Cock et al., 2013a & 2013b).

PURPOSE OF PAPER

The following paper describes potential benefits from the transition of intravenous Rituximab to subcutaneous Rituximab with the intention of reducing time spent in a cancer facility, reducing cost, decreasing health provider time, and improving efficiency in cancer care delivery systems. Physicians, nurses and administrators take feasible measures to reduce wait times so that patients do not have to spend excess time in health care facilities. Ideas such as altering scheduled clinic appointments have assisted treatment areas to run more smoothly and efficiently. However, this is not always convenient or effective in resolving over-capacity issues. In order to improve efficiency in the delivery system, there is a need to investigate other novel approaches. One such approach is the transition from intravenous Rituximab to subcutaneous Rituximab. However, there are inherent challenges in this transition.
Approval and access of cancer pharmaceuticals in Canada is one of the greatest challenges and a lengthy process. Between the years of 1994 and 2008, 12 new cancer drugs were approved worldwide (Turner, 2008). At that time, Canada’s median lag time for drug approval by Health Canada was 0.8 years when comparing approval time in Canada and approval anywhere else in the world (Turner, 2008). Part of this delay was because manufacturers submit their request for approval to larger markets (U.S., U.K., and Germany) first, allowing these countries shorter timelines to approval (Turner, 2008). Once approval by Health Canada is obtained, an oncology drug review board and each province evaluate the drug based on their own evaluation process. Due to variation of approval processes and approval times among Canadian provinces, access to cancer pharmaceuticals can take years longer than in other settings or not occur at all (Turner, 2008).

Additionally, approval of a drug does not guarantee approval for any route of administration. This explains why Rituximab cannot be given subcutaneously in Alberta (AHS, 2013). Based on the pharmacokinetic (PK) results of several trials (outlined below) and a cost analysis, there is evidence to support the transition to subcutaneous Rituximab while ensuring efficacy and optimal cancer treatment (Assouline et al., 2012; Davies, et al., 2014; De Cock et al., 2013b; Salar et al., 2013). Highlights from these studies will be presented below (also see Table 1).

Subcutaneous Rituximab: Time and motion Study in eight countries

De Cock et al. (2013a & 2013b) performed a time and motion study compiled by 23 centres from eight different countries: (Italy [IT], Russia [RU], Slovenia [SL], United Kingdom [U.K.], Spain [SP], France [FR], Austria [AU] and Brazil [BR]). Their time and motion study reports the estimated reduction in total health care provider time associated with the transition to subcutaneous Rituximab ranged from 0.9 hours (AU) to 5.1 hours (U.K.) (De Cock et al., 2013b). The differences in mean chair time saved with the subcutaneous over the intravenous administration ranged from 126.1 minutes (64% in SL) to 280.1 minutes (86% in IT) (De Cock et al., 2013b). A reduction in pharmacy health care provider time is reported as ranging from 27% in Spain, to as high as 57% in Russia (De Cock et al., 2013b). Finally, De Cock et al. (2013b) report as a key finding based on the mean chair time saved, if these findings were simulated for a hypothetical centre treating 50 patients for nine sessions annually (six induction and three maintenance), a total chair time savings with subcutaneous Rituximab would range from approximately 105.1 (Slovenia) to 233.4 (Russia) eight-hour days. They conclude their results support the switch from intravenous Rituximab to subcutaneous Rituximab because it leads to substantial reductions in administration time (nursing time), relative reduction in mean chair time, and reduced active health care provider time (pharmacy prep time). All reductions lead to an increased ability to improve the number of other patients that can be treated and the overall efficiency of a cancer facility (De Cock et al., 2013b).

Cost analysis of subcutaneous versus intravenous Rituximab

The cost of Rituximab is reported as variable from province to province in the literature (Griffiths, Gleeson, Mihael, & Danese, 2012). Rituximab cost in Canada is reported as high as $34,000 per treatment course (eight cycles) (Gazette, 2008). Based on an average BSA of 1.7 m², the average cost of intravenous Rituximab using a standard dose of 375 mg/m² (637 mg) is $4,250.00 ($6.67/mg) (Griffiths et al., 2012). From this calculation, for a fixed dose of Rituximab 1,400 mg via subcutaneous route the cost is $9,340.66. Finally, a fixed dose of 1,600 mg of subcutaneous Rituximab would cost $10,675.04.

A further drawback to the subcutaneous route of Rituximab is that the formulation is best delivered along with a recombinant human hyaluronidase enzyme (Frost, 2007). The space outside the adipocytes in the hypodermis is not a fluid, but a solid extracellular matrix (Frost, 2007). This extracellular matrix limits the volume of drug that can be delivered at a single injection site necessitating the recombinant human hyaluronidase enzyme (Frost, 2007). This is a biochemically prepared enzyme used to increase absorption at the site in the extracellular matrix (Frost, 2007). The actual cost of this additive is not known by this author, but provides some additional insight into the significant cost related to the subcutaneous Rituximab. Despite the cost of the drug being significantly higher for the subcutaneous route, the other surrounding factors that need to be considered for this novel approach to reveal its benefit are highlighted below (De Cock et al., 2013b).

The administration of intravenous Rituximab generally is scheduled as a next-day treatment. This route of administration requires premedication, IV supplies, substantially more health care provider monitoring time, and is associated with an increased risk of hypersensitivity (AHS, 2013, Biogen Idec and Genentech, 2006,. De Cock et al., 2013a & 2013b). The cost of premedications (Diphenhydramine, Acetaminophen, Hydrocortisone and Ranitidine) associated with the administration of intravenous Rituximab is approximately as high as $14.20 per treatment (BARD, 2014). Given subcutaneously, Rituximab has essentially no associated costs involved regardless of the amount of fixed dose administered.

Health care provider time (nursing)

Health care provider (nursing) preparation time is further associated with an increased related cost if the Rituximab is administered intravenously (De Cock et al., 2013a & 2013b). Based on a mid-scale wage of a registered nurse in Alberta of $40.00/hour and an approximate preparation time of 20 minutes (to start an easy intravenous, prime lines, mix and hang Diphenhydramine, Hydrocortisone and give oral Acetaminophen), an approximate cost of $13.33 per treatment (tx) is calculated (United Nurses of Alberta [UNA], 2013). There is no associated cost related to health care provider (nursing) preparation time with the administration of subcutaneous Rituximab, as a nurse does not use preparation time. For the purpose of this analysis, independent double-checking
**AUC is the area under the curve in a plot concentration of drug in blood plasma against time (Mao et al., 2013).**

*C-trough: Based on a PK model predicted C trough levels of SC Rituximab 1600mg were comparable to IV dose of 500 mg/m² --- 75.2 ug/ml (in SC group) vs 62.5 ug/ml (in IV group).

**Area under the curve (AUC): Using the same PK model above 1600mg SC Rituximab was non-inferior to standard IV dose used in CLL patients of 500 mg/m².

Side effects reported as low grade intensity however high frequency in all three arms of SC dosing. Grade 1 and 2 mild local injection site reactions including mild pain and erythema, puritis, chills and vomiting with subcutaneous Rituximab. Both *C trough + **AUC levels in SC Rituximab group show non-inferiority to the group receiving standard dosing IV Rituximab. Followup questionnaire indicates both nurses (94.5%) and patients (92.7%) prefer SC route of administration.

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<td>Salar, Avivi, Larouche, Janikova, Pereira, Brewster, Catalan, McIntyre, Sayyad and Hanes</td>
<td>Multicenter, randomized, open label non-inferiority, comparing IV vs SC Rituximab</td>
<td>All patients received at least one dose of IV Rituximab then were randomized to either the IV or SC arm. In addition all received a standard 8 cycles of CHOP or CVP chemotherapy.</td>
<td>Adult patients (&gt;18y) Histologically confirmed CD20+ grade 1, 2, 3a follicular lymphoma.</td>
<td>Rituximab concentration on Day 28 in Non Hodgkins Lymphoma patients administered 625 mg/m² SC were comparable to those in patients administered the standard dose of IV Rituximab 375 mg/m².</td>
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<td>Davies, Merli, Mihaljevic, Siritanaratkul, Solal-Celigny, Barrett, Berge, Bittner, Boehnke, McIntyre and MacDonald</td>
<td>2 stage and in the second stage of accrual Phase 3 international randomized, controlled, open label study Purpose: to assess a fixed dose of 1400mg SC Rituximab was pharmacokinetically inferior to the standard intravenous dose of 375 mg/m² and to investigate if SC route would impair Rituximab’s anti-lymphoma activity Stage 1: Randomized 1:1 standard CHOP or CVP +/- Rituximab 1400mg SC or 375 mg/m² IV. One induction of IV Rituxan followed by allocation to either arm in cycles 2–8. Patients with partial or complete response continued on with IV or SC Rituximab as maintenance every 8 weeks for 2 years.</td>
<td>Consented eligible adults &gt;18 years old CD20+ grade 1, 2, 3a follicular lymphoma ECOG 0–2 with measurable disease on CT or MRI.</td>
<td>Mean *C trough levels were higher in the SC group (134.58 ug/ml) vs. the IV group (83.13 ug/ml) showing non-inferiority in the SC group. ORR 54% (IV+chemo) vs 57% (SC+chemo). CR 19% (IV+chemo) vs 29% (SC+chemo). PR 35% (IV+chemo) vs 37% (SC+chemo). Baseline CD19+ lymphocyte counts were measured: 0.12 x 10E9 cells/L in SC group vs 0.05 x 10E9 cells/L in IV group. Before cycle 2 dosing median count of CD19+ lymphocytes were 0 cells/L and B cell depletion was maintained throughout the treatment.</td>
<td>SC dosing: side effects related to administration (injection site reaction) reported as low grade intensity however high frequency at 31%. Higher incidence of neutropenia (grade 3 and 4) was reported in both groups IV 22% vs SC 26%.</td>
<td>After cycle 7 of induction, SABRINA showed non-inferiority *C trough levels and switching to SC Rituximab does not appear to affect the anti-lymphoma activity of Rituximab No new safety concerns related to side effects were found with the Subcutaneous administration.</td>
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Table 1: Review of the trials

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*C-trough refers to the minimum serum drug concentration during a given dosing interval (Mao et al., 2013). **AUC is the area under the curve in a plot concentration of drug in blood plasma against time (Mao et al., 2013).
of the drug is not taken into consideration for either route of administration, as the cost would be equivalent. The cost of nursing administration time is significantly higher for intravenous administration versus subcutaneous administration. Rituximab given intravenously for the initial dose is approximately four to six hours of time (Biogen Idec and Genentech, 2006). If tolerated well, subsequent doses can be administered over 90 minutes (Biogen Idec and Genentech, 2006). Based on a mid-scale wage of an Alberta registered nurse ($40.00/hr) the cost of administering intravenous Rituximab initial and subsequent doses are $240.00/tx and $60.00/tx respectively (UNA, 2013). Administration of the drug includes continuous monitoring of the patient, taking vital signs, and documentation. Although this calculation is based on one RN, in an outpatient treatment area, historically, the expectation is for two nurses to be present at all times in the event a hypersensitivity reaction occurs. This second RN is not accounted for in this uncomplicated analysis, as this cost would only be incurred in the event of an emergency. The administration of subcutaneous Rituximab is cited as taking on average approximately 15 minutes of active health care provider time (nursing) (De Cock et al., 2013a). Based on a mid-level registered nursing wage of $40.00/hr, the associated cost of subcutaneous administration of Rituximab is significantly lower and is calculated at less than $10.00/tx (UNA, 2013). This is significant for more than the reason of cost. Administering Rituximab subcutaneously has the benefits of less health care provider (nursing) preparation and administration time, and there are no reported risks of hypersensitivity reactions that are associated with it for the patient (De Cock et al., 2013a & 2013b).

**Cost of supplies**

When administering intravenous Rituximab several supplies are needed that incur a greater cost than subcutaneous Rituximab (Baxter, 2014). These supplies include equipment to start the intravenous (i.e., alcohol swabs, gauze, clear IV cover, tape, IV cannula, and a tourniquet), intravenous lines (i.e., Interlink solution sets and NS IV bags) to administer the drug, and a Baxter pump to accurately monitor the flow rate (Baxter, 2014). The calculated cost of supplies for one initial/subsequent intravenous infusion of Rituximab is $24.35/tx and $22.77/tx respectively (Baxter, 2014). The number of times one intravenous pump can be utilized in an eight-hour day for an initial treatment and a subsequent treatment of Rituximab is calculated on an annual basis to obtain these figures. There is much less cost associated with the administration of subcutaneous Rituximab. The cost associated with the supplies needed to administer Rituximab subcutaneously (alcohol swabs, syringe, needle, band aid) is approximately $0.29/tx (Baxter, 2014). This is a significant reduction in cost. This again supports the beneficial transition from intravenous Rituximab to subcutaneous Rituximab.

**Health care provider time (pharmacy)**

Health care provider time (pharmacy) associated with the preparation of the drug is roughly estimated. Based on an average Alberta pharmacists’ wage of $50.00/hour and a projected time of 12.5 minutes to prepare the standard intravenous dose (375 mg/m^2) of the drug (including calculations and preparation of the drug and independent double checking time), the estimated cost associated is $10.41 per treatment (Government of Alberta, 2014). Subcutaneous Rituximab is given as a fixed dose of 1,400 mg (and not based on BSA) and the drug is available in ready-to-use formulation without the need for reconstitution (Roche, 2014). Therefore, the needed time for BSA calculation is omitted. In De Cock et al.’s (2013) time and motion study, it is cited that Rituximab subcutaneous is associated with reductions in health care provider time in the pharmacy ranging from 37% in Slovenia to 65% in Russia. This decreases the time spent (37%–65%) preparing the drug in the pharmacy from 12.5 minutes to as much as 4.38–7.88 minutes. This time reduction is furthermore associated with decreased cost from $10.41 (intravenous) to $3.64–5.56 (subcutaneous) dollars to prepare one treatment, again based on a pharmacist wage of $50.00/hr (Government of Alberta, 2014).

**Associated risks to the health care provider**

An obvious risk associated with both routes of administration of Rituximab is a needle stick injury. It is cited as much as $2,000 (including administrative reporting cost, cost of initial MD visit, and cost of prophylaxis) to initially care for a health care provider who has been injured by a needle stick (Medical Technology Association of Australia [MTAA], 2013). The cost to treat a health care provider who becomes infected with a blood borne virus is large and difficult to assign a concrete number to, as legal costs vary (Jagger, Hunt and Pearson, 1990; MTAA, 2013). As most cancer patients have difficult veins to access due to the amount of chemotherapy they receive, it is likely they would endure more than one attempt to start an intravenous to receive their Rituximab. Given this likelihood, it is further purported that the risk of a needle stick injury would inevitably be higher if the drug is administered intravenously versus given subcutaneously (MTAA, 2013).

**Bed/chair time savings**

A significant factor in the transition of intravenous Rituximab to subcutaneous Rituximab is the saving of time spent in a bed or chair by the patient (De Cock et al., 2013a & 2013b). De Cock et al. (2013b) report a difference in mean chair (bed) time saved with subcutaneous over intravenous administration ranging from 126.1 minutes in Slovenia to 280.1 minutes in Italy. This is significant in a busy cancer centre faced with an excessive number of cancer treatments relative to the amount of space available. De Cock et al. (2013b) simulate these findings to a hypothetical cancer centre treating 50 patients for nine sessions (six induction and three maintenance) annually and suggest that the amount of chair/bed time freed would range from 105.1 (in Slovenia) to 233.4 (in Italy) eight-hour days. The total cost of this is difficult to assign a value. However, if an addition of 105.1–233.4 eight-hour days were added annually to any health care delivery system, it is certain the savings in health care provider wages alone would show substantial benefit. Based on a mid-scale wage of one Alberta registered nurse of $40.00/hour for an eight-hour day, a savings of $33,600 (105 days) and $74,560 (233 days) respectively
can be projected or allocated to caring for other patients in the treatment room (UNA, 2013). This savings in time is not only beneficial for a cancer centre, it would give cancer patients the added convenience and benefit of time to spend elsewhere with their loved ones rather than in a treatment facility (Assouline et al., 2012; Aue et al., 2010; De Cock et al., 2013a & 2013b).

Quality of life
When faced with a cancer diagnosis, time is precious to cancer patients and their families. In fact, a price tag cannot be placed on giving the gift of time to someone dying. Any measure taken to gain quality time significantly improves the quality of life for patients and families. Transitioning from intravenous to subcutaneous administration of Rituximab is one measure to accomplish this (Assouline et al., 2012; De Cock et al., 2013a & 2013b; Roche, 2012). Alberta cancer patients will receive the greatest benefit from this transition, as their time spent in the cancer centre will be significantly reduced from hours to minutes whilst still receiving optimal treatment for their cancer (Assouline et al., 2012; Aue et al., 2010; De Cock et al., 2013a & 2013b; Roche, 2012). Davies et al. (2014) report the median injection time for subcutaneous Rituximab was 6.1 minutes. An intravenous Rituximab infusion takes several hours and is associated with greater risks and more grade 3 and 4 adverse events (Davies et al., 2014). As stated earlier in the paper, the risk of hypersensitivity associated with intravenous Rituximab is substantially higher, necessitating a need for prophylactic premedications to prevent this occurrence. This risk can be mitigated by the transition to subcutaneous Rituximab. It is noteworthy that subcutaneous Rituximab has a reportedly higher incidence of adverse events. However, the intensity of the events reported is much lower (Assouline et al., 2012; Davies et al., 2014). Assouline et al. (2012) further report grade 1 and 2 mild local injection site reactions including mild pain and erythema, puritis, chills, and vomiting with subcutaneous Rituximab. Davies et al. (2014) further report grade 3 and 4 neutropenia is associated with both IV (22%) and SC (26%) Rituximab putting patients at greater risk for serious adverse events including febrile neutropenia. Although both routes of administration have some type of adverse event, I suspect cancer patients would choose the route that involves the least amount of time with the least severe side effects. Currently, there are no quality-of-life studies related to subcutaneous Rituximab. However, it is documented in United States-based studies there are plans to measure this concept in current ongoing trials. There are Canadian studies (Victoria, Hamilton, and Montreal) in the accrual phase regarding patient preference between intravenous and subcutaneous Rituximab with Diffuse Large B-cell Lymphoma (DLBCL) and Follicular lymphoma (Canadian Partnership Against Cancer, 2014). As well, there is a Canadian study underway comparing subcutaneous and intravenous Rituximab in combination with CHOP chemotherapy in previously untreated CD20+ DLBCL (Canadian Partnership Against Cancer, 2014).

CONCLUSION
Although there are trials in Canada evaluating subcutaneous Rituximab, there are none in Alberta (Canadian Partnership Against Cancer [CPAC], 2014; Hoffman-La Roche, 2014). Four trials in eastern Canada were cited comparing intravenous to intravenous Rituximab plus CHOP chemotherapy in the setting of Diffuse Large B-cell Lymphoma (CPAC, 2014; Hoffman-LaRoche, 2014). There are further studies mentioned above evaluating patient preferences between intravenous and subcutaneous Rituximab. Current American trials to date show benefits of transitioning from intravenous to subcutaneous Rituximab. These benefits include reduced wait times, reduced health care provider time related to administration and preparation time, use of fewer supplies, and increased availability of space for other patients needing cancer treatments. Benefits translate into improving efficiency in a cancer centre and ensuring efficacy and optimal treatment for the patient’s disease (Assouline et al., 2012; Davies et al., 2014; De Cock et al., 2013; Salar et al., 2012). Limitations of this transition include cost, approval and access.

REFERENCES


